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F. G. POPE

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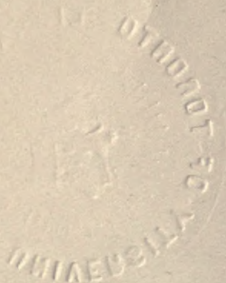(UNIVERSITY OF LONDON)
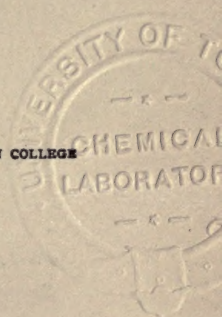
WITH 261 DIAGRAMS

SECOND EDITION

First Published . . *September 19th, 1912*
Second Edition . . *1919*

CONTENTS

INTRODUCTION

IN the course of the past century the study of organic chemistry has been pursued with an energy which has not been exceeded in any department of science, and, by sustained effort, not only has a better insight been obtained into processes of life, but many branches of industry have been revolutionized. It is common knowledge that much of the distinction between Inorganic and Organic Chemistry was broken down by Wöhler's discovery of the artificial production of urea in 1828, and although the breach in the barrier between the two branches of the science has been continually widened, the convenience of a division into inorganic and organic chemistry is such, that the study of the carbon compounds would probably remain distinct, even if it were not necessitated by the extreme complexity of the subject. At the same time, the organic chemist avails himself to an increasing extent of physical methods of research, and the use of organic derivatives in solving problems of inorganic chemistry, especially those relating to valency and spatial arrangement, becomes continually more widespread. Organic chemistry, in the stricter sense of the term, still offers a vast number of problems for solution; with the rapid progress made, the problems of one decade become the commonplaces of the next, and it is worth while to take an occasional general survey, considering the lines in which immediate progress is probable.

In the eighteenth century the chief recognized characteristics of organic compounds were that they contained aqueous and combustible principles. Lavoisier's explanation of combustion directed the attention of chemists to the fact that organic compounds always contain carbon, and generally hydrogen in addition; these elements furnish carbonic acid and water respectively when

the compounds in question are burnt. Following up this discovery, Lavoisier devised a method for the determination of carbon in organic compounds, and somewhat later collected the water formed during combustion by absorbing it with a deliquescent salt. Considerable ingenuity was expended during the early part of the nineteenth century in perfecting the methods of organic analysis, and it soon became possible to determine the composition of a carbon compound with the accuracy attained in a mineral analysis.

The increasing number of organic compounds of known composition rendered the introduction of some system necessary. At a relatively early date, Dumas and Boullay compared the ethyl compounds with the addition products formed by ammonia; ethyl alcohol was the hydrate of "bicarburetted hydrogen," $C_2H_4.H_2O$, and analogous to aqueous ammonia, $NH_3.H_2O$; ethyl chloride and ammonium chloride were regarded respectively as the hydrochlorides of bicarburetted hydrogen and ammonia, and similar comparisons were instituted between other ethyl and ammonium compounds.

The idea of compound radicals was introduced by Lavoisier and Guyton de Morveau at a time when sugar was supposed to be the neutral oxide of a hydrocarbon radical, whilst oxalic acid was the higher acidic oxide obtained on oxidation with nitric acid. In 1832, Liebig and Wöhler published their research on the radical of benzoic acid; not only was it shown that *benzoyl* formed an integral part of a large series of compounds, but the fact was recognized that oxygen might be a constituent of a compound radical. A year or two later Liebig pointed out that order might be introduced amongst the compounds derived from alcohol if ether were looked on as the oxide of a radical "ethyl"; alcohol would then be the hydrate of this oxide, whilst the various ethers (or esters, as they are now called) are the analogues of metallic salts. Dumas adopted the idea of compound radicals, which also appealed in many of its aspects to Berzelius; the discovery of substitution processes had, however, at first a retarding influence. With a fuller understanding of the manner in which substitution

takes place and the introduction of the theory of types, the way was paved for the idea of molecular structure, and research in this direction made rapid progress after the complete recognition of Avogadro's law.

In the development which led to the adoption of molecular and structural formulæ, Frankland, Gerhardt, Hofmann, Laurent, Odling, Williamson, and Wurtz were specially prominent; to Kekulé must be assigned the credit of having first recognized the tetravalency of carbon, a similar view being put forward by Couper shortly afterwards.

The idea of the tetravalency of carbon led Kekulé to his conception of the structure of the aromatic compounds (1865), and although various modified formulæ have been proposed for benzene, the original idea that the six carbon atoms are members of one closed ring still holds its own. By 1870 the essential foundations of structural organic chemistry had been laid, and meanwhile the structure of the aromatic compounds had assumed large proportions, an added incentive to the work being found in the possibility of obtaining commercially valuable products. Rarely has an industry contributed so greatly to the advancement of science as in the case of the artificial organic dyestuffs.

During the next two decades the preparation of new organic compounds and the synthesis of natural products occupied the attention of the greater number of organic chemists, and some remarkable successes were achieved. Alizarine and indigo were obtained artificially; towards the end of the "eighties" the constitution of glucose was ascertained with some degree of certainty, and the synthesis of various sugars by Emil Fischer must give rise to as much admiration to-day as when the researches were first published.

Meanwhile other classes of naturally occurring compounds had been extensively investigated, and the derivatives of uric acid, caffeine, etc., from the (at that time) hypothetical parent substance, purine, assured. It was not, however, until Emil Fischer had virtually concluded his sugar work that he turned his attention to the purine group once more, and in a series of brilliant researches

synthesized the most important naturally occurring derivatives, the previous syntheses of uric acid by Horbaczewski and Behrend in no way lessening the value of the results obtained. Fischer's researches on the constitution of the sugars, the purine compounds, and the products of the hydrolysis of the proteins, followed up by the syntheses of so many substances of these groups, has afforded a sound basis for biological chemistry.

Another group of compounds, the terpenes, had also attracted much attention, and camphor had been shown to possess a closely related structure. Despite the useful experimental material accumulated by the researches of Armstrong, Tilden, Wallach, and others, the constitution of these compounds remained uncertain, Bredt's happy idea of the structure of camphor led to renewed effort, and in a few years the constitution of most of the natural hydrocarbons and cyclic ketones was settled. Syntheses in the terpene series are largely due to W. H. Perkin; for not only has he achieved the actual artificial production of such compounds, but the methods by which the formation of closed carbon chains can be effected are chiefly the results of his work. The chemistry of this series of compounds owes not a little to chemical industry, the synthesis of artificial perfumes having proved a remunerative field industrially.

The alkaloids have occupied many workers since the early days of organic chemistry, and at the present time the structure of a large number of these substances is known with accuracy, or with a considerable degree of probability; at the same time the examination of natural organic dyestuffs has led to much systematic research concerning compounds whose molecule contains a pyrone ring.

Whilst all this strictly organic work was in progress, other investigators followed a different line, endeavouring to trace relationships between the physical properties of substances and their chemical constitution. In the early days of this type of work, inorganic substances received possibly rather more than their fair share of attention; it might perhaps be contended that latterly the pendulum had swung too far in the other direction.

Certainly organic compounds offer one immense advantage : there is usually no doubt either as to the molecular weights or the arrangement of linkages in the substances under investigation. Prosecution of researches of this character has led to striking advances ; our ideas as to the arrangement of atoms in space and the rearrangement of structure which often occurs on salt formation have undergone considerable change. Workers in this branch of science are occasionally unduly optimistic, but the success which has attended some of the attempts to refer properties to constitution, notably in the cases of molecular volume and molecular refraction, can only act as a greater incentive to work. Organic chemists have achieved much, and as the habit of simply recording the melting-points and analytical data of new compounds dies out, it will be more clearly recognized what an enormous field of work lies in front of us.

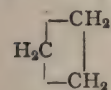J. T. HEWITT

ABBREVIATIONS USED IN THE BIBLIOGRAPHY

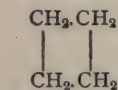| ABBREVIATION			FULL TITLE
Amer. Chem. Jour.	.	.	American Chemical Journal.
Ann.	.	.	Justus Liebigs' Annalen der Chemie.
Ann. Chim. Phys.	.	.	Annales de Chimie et de Physique.
Arch. Pharm. .	.	.	Archiv. der Pharmazie.
B. A. Rep. . .	.	.	British Association Reports.
Ber.	.	.	Berichte der deutschen chemischen Gesellschaft.
Bull. Soc. . .	.	.	Bulletin de la Société chimique de France.
C. R. . . .	.	.	Comptes rendus hebdomadaires des Séances de l'Academie des Sciences.
Gazz. . . .	.	.	Gazzetta chimica italiana.
J. Amer. Chem. Soc.	.	.	Journal of the American Chemical Society.
Jour. Chem. Soc. .	.	.	Transactions of the Chemical Society.
Jour. prak. Chem. .	.	.	Journal für praktische Chemie.
Jour. Russ. phys. chem. G.	.	.	Journal of the Physical and Chemical Society of Russia.
Monats. . . .	.	.	Monatshefte für Chemie und verwandte Theile anderer Wissenschaften.
Phil. Mag. . .	.	.	Philosophical Magazine.
Proc. Chem. Soc. .	.	.	Proceedings of the Chemical Society.
Z. f. Elektrochem.	.	.	Zeitschrift für Elektrochemie.
Z. f. phys. Chem. .	.	.	Zeitschrift für physikalische Chemie.

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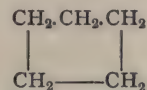
CHAPTER I

THE POLYMETHYLENES

THE isolation of trimethylene in 1882 by Freund led to the opening up of a vast field of research, since it showed that a series of cyclic compounds existed which could not be regarded as simple derivatives of benzene. The simple hydrocarbons of the group consist of three or more methylene groups united so that they form a closed chain, the names given to the various members (*e.g.* trimethylene, tetramethylene, etc.) denoting the number of methylene groups associated together in the particular ring so designated, thus:—
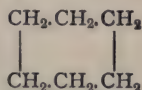

|			
$H_2C\begin{cases} -CH_2 \\ -CH_2 \end{cases}$	$\begin{matrix} CH_2.CH_2 \\ \| \quad \| \\ CH_2.CH_2 \end{matrix}$	$\begin{matrix} CH_2.CH_2.CH_2 \\ \| \qquad \| \\ CH_2----CH_2 \end{matrix}$	$\begin{matrix} CH_2.CH_2.CH_2 \\ \| \qquad \| \\ CH_2.CH_2.CH_2 \end{matrix}$
Trimethylene	Tetramethylene	Pentamethylene	Hexamethylene

although under a more systematic scheme of nomenclature they are spoken of as *cyclopropane, cyclobutane, cyclopentane*, etc. The unsaturated members of the series are best named according to the Geneva system in which the suffix *-ane* is replaced by *-ene*, *-diene*, or *-triene*, according to the number of double linkages present in the molecule, the position of such double linkages being shown by the numerals immediately following the suffix, thus:—

1. $H_3C.C = CH.C.CH_3$ 3

6. $CH_2.C(CH_3).CH$ 4
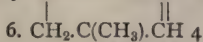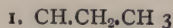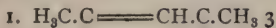
Trimethyl—1.3.5 ; cyclohexadiene—1.3

1. $CH.CH_2.CH$ 3

5. $CH —— CH$ 4

Cyclopentadiene—3.5

As an alternative method for denoting the position of the double

linkages, Baeyer's symbol $\triangle$ is occasionally used, being placed in front of the name of the compound and immediately followed by one or more numerals indicating the position of the double linkages in the molecule—
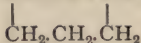
<div>

1. HOOC.CH.CH : CH 3.
    | |
  CH₂.CH₂.CH₂

$\triangle$ 2. Tetrahydrobenzoic acid

1. HOOC.C : CH—CH 3.
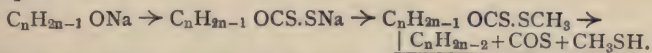 | ||
  CH₂.CH₂.C.COOH
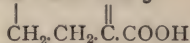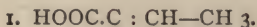
$\triangle$ 1.3. Dihydroterephthalic acid

</div>

In the production of the polymethylene compounds it is found that the five and six membered rings are the most stable of the series, and are preferentially formed.   The reason for this greater stability was first shown by Baeyer in his "Spannung's Theorie," which refers the phenomena to stereo-chemical data. In this theory, Baeyer accepts the generally received laws as to the affinities of the carbon atom, and adds the following assumption : " The four valencies of a carbon atom act along the direction joining the centre of a tetrahedron with the corners of the tetrahedron, and make, with one another, angles of $109°.28'$. The direction of the attraction can, however, experience a deviation, and this gives rise to a tension which increases with the magnitude of the deviation."   Applying this principle to the polymethylene compounds, it is obvious that the deviation must vary with the particular group considered, and it is possible to calculate the deviation in the various cases if one assumes each axis to experience an equal displacement.   Thus in C_2H_4, with one double bond, each must undergo a deviation $\frac{1}{2}$ $(109°.28') =$ $54°.44'$; in C_3H_6 (trimethylene), which can be considered as possessing the equilateral triangle configuration for the plane of its carbon atoms, the deviation must be $\frac{1}{2}$ $(109°.28' - 60°) = 24°.$ $44'$, whilst in tetramethylene, pentamethylene, hexamethylene, and heptamethylene the respective deviations will be $\frac{1}{2}$ $(109°.28'$ $- 90°) = 9°.44'$; $\frac{1}{2}(109°.28' - 108°) = 0°.44'$; $\frac{1}{2}(109°.28' - 120°) =$ $- 5°.16'$; $\frac{1}{2}$ $(109°.28' - 128°.34') = - 9°.33'$.   Consequently the deviation, and therefore the strain, is least in the penta- and hexamethylene compounds, and these should be the most stable. This theory fits in very well with the observed facts; thus ethylene, which forms the weakest ring, is immediately acted upon by bromine and even iodine, while the trimethylene ring is

readily attacked by hydrobromic acid, and even by bromine in
the presence of sunlight. Tetramethylene derivatives are, on the
other hand, more stable, whilst the penta- and hexamethylene
derivatives are remarkably stable, and show little or no tendency
to rupture of the molecule.

GENERAL METHODS OF PREPARATION

The hydrocarbons of the series may be obtained by the action
of sodium on the alkylene dibromides, which have not the
halogen atoms attached to the same or to neighbouring carbon
atoms. Cyclic ketones, by conversion into alcohols, and then
into the corresponding iodo-derivatives, also yield hydrocarbons
when these halides are reduced by means of zinc and acid
(Wislicenus). In the cyclohexane series some members may be
obtained by the direct reduction of the benzene hydrocarbons
with sodium and alcohol, or the method of Sabatier and Sen-
derens may be employed, in which case the vapour of the benzene
hydrocarbon is passed along with hydrogen, over reduced nickel,
at a temperature of 180-250° C. In the preparation of unsaturated
hydrocarbons, the important xanthogenic ester method of Tschu-
gaeff may be used, in which case the cyclic monohydric alcohol
is converted into the sodium derivative (or preferably the potassium
derivative), and this is then transformed into the sodium xantho-
genate by the direct action of carbon bisulphide. On treatment
with an alkyl iodide the xanthogenic ester is produced, and on dis-
tillation decomposes with formation of the unsaturated hydro-
carbon, which is then generally purified from final traces of
sulphur compounds by redistillation over sodium. The reaction
takes place thus :—

$$C_nH_{2n-1}\,ONa \rightarrow C_nH_{2n-1}\,OCS.SNa \rightarrow C_nH_{2n-1}\,OCS.SCH_3 \rightarrow$$
$$| \;\; C_nH_{2n-2} + COS + CH_3SH.$$

In some cases the elimination of water from a cyclic alcohol can
be carried out either by heating the alcohol with anhydrous
oxalic acid or with potassium bisulphate, with the consequent
formation of the unsaturated hydrocarbon ; or the hydrochloride
of a cyclic amine may be distilled when it decomposes, in some
cases with elimination of ammonium chloride and formation of
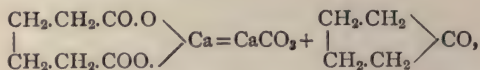
the hydrocarbon.   In this way Baeyer obtained carvestrene from vestrylamine hydrochloride and from carylamine hydrochloride.

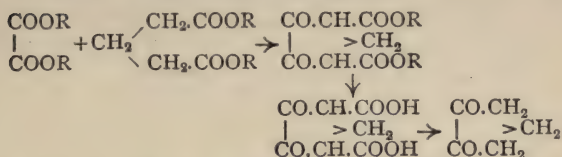$$C_{10}H_{17}NH_2.HCl = NH_4Cl + (1)CH_2.C_6H_6.C_3H_7.(4).$$
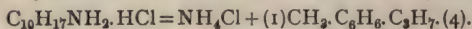
The methods employed in the formation of the alcohols of the series are essentially the same as those adopted in the formation of the aliphatic alcohols, namely, the replacement of halogen in halogen derivatives of the hydrocarbons by the hydroxyl group by means of silver oxide and water, or by the use of silver acetate followed by hydrolysis of the ester produced; by the reduction of ketones; by Bouveault and Blanc's recently discovered method of the reduction of esters by sodium and alcohol,

$$R.COOC_2H_5 + 4H = R.CH_2OH + C_2H_5OH ;$$
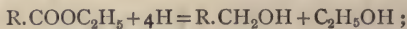
by the action of nitrous acid on the cyclic amines, and by the addition of the elements of water to the unsaturated cyclic hydrocarbons, the latter reaction being brought about in many cases simply by boiling the hydrocarbon with dilute sulphuric acid.   Wagner has also made the important discovery that di-hydric alcohols of the series may be obtained in very good yield when the unsaturated compounds are oxidized by means of a very dilute solution of potassium permanganate in the presence of a dilute solution of the alkaline hydroxides at low temperature. For the methods of preparation of the ketones we are indebted to the researches of J. Wislicenus, who showed that the distillation of the calcium salts of the higher dibasic acids of the oxalic series gave rise to these substances, calcium adipate for example, yielding keto-pentamethylene,

$$\begin{matrix} CH_2.CH_2.CO.O \\ | \\ CH_2.CH_2.COO. \end{matrix} \Big\rangle Ca = CaCO_3 + \begin{matrix} CH_2.CH_2 \\ | \\ CH_2.CH_2 \end{matrix} \Big\rangle CO,$$

whilst calcium pimelate and calcium suberate yield ketohexamethylene and ketoheptamethylene respectively, although in these two latter cases the yield is not so good as in the former case; and to Dieckmann, who condenses ethyl oxalate with the esters of dibasic acids in the presence of sodium ethoxide, the resulting esters on hydrolysis and elimination of carbon dioxide yielding diketones.

$$\begin{array}{l}\text{COOR}\\|\\\text{COOR}\end{array} + CH_2 \begin{array}{l}\diagup CH_2.COOR\\\diagdown CH_2.COOR\end{array} \rightarrow \begin{array}{l}\text{CO.CH.COOR}\\|\quad>CH_2\\\text{CO.CH.COOR}\end{array}$$

$$\downarrow$$

$$\begin{array}{l}\text{CO.CH.COOH}\\|\quad>CH_2\\\text{CO.CH.COOH}\end{array} \rightarrow \begin{array}{l}\text{CO.CH}_2\\|\quad>CH_2\\\text{CO.CH}_2\end{array}$$
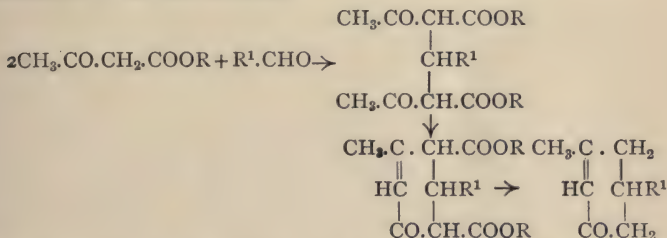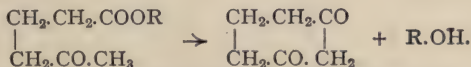
A somewhat similar reaction takes place on treatment of the esters of acids of the adipic and pimelic series with sodium.

$$\begin{array}{l}CH_2.CH_2.CH_2.COOR\\|\\CH_2.CH_2.COOR\end{array} \rightarrow \begin{array}{l}CH_2.CH_2.CH.COOR\\|\qquad\quad|\\CH_2.CH_2.CO\end{array}$$

$$\downarrow$$

$$\begin{array}{l}CH_2.CH_2.CH.COOH\\|\qquad\quad|\\CH_2.CH_2.CO\end{array} \rightarrow \begin{array}{l}CH_2.CH_2.CH_2\\|\qquad\quad|\\CH_2.CH_2.CO\end{array}$$
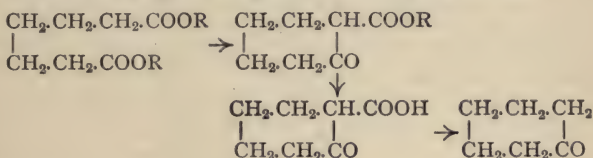
As alternative methods, Knoevenagel has shown that the condensation of aceto-acetic ester with aldehydes leads to the formation of unsaturated ketonic acid esters, from which the corresponding ketones may be obtained by saponification and elimination of carbon dioxide,

$$2CH_3.CO.CH_2.COOR + R^1.CHO \rightarrow \begin{array}{l}CH_3.CO.CH.COOR\\|\\CHR^1\\|\\CH_2.CO.CH.COOR\end{array}$$

$$\downarrow$$

$$\begin{array}{l}CH_3.C . CH.COOR\\\|\qquad|\\HC\quad CHR^1\\|\qquad|\\CO.CH.COOR\end{array} \rightarrow \begin{array}{l}CH_3.C . CH_2\\\|\qquad|\\HC\quad CHR^1\\|\qquad|\\CO.CH_2\end{array}$$

and Vörlander, by the action of sodium ethoxide on esters of δ-ketonic acids, has obtained diketones of the hexamethylene series

$$\begin{array}{l}CH_2.CH_2.COOR\\|\\CH_2.CO.CH_3\end{array} \rightarrow \begin{array}{l}CH_2.CH_2.CO\\|\qquad\quad|\\CH_2.CO. CH_2\end{array} + R.OH.$$

Blanc has recently shown that cyclic ketones may be obtained from the corresponding adipic or pimelic acids by heating them with acetic anhydride, and subsequently distilling the anhydrides which are so formed, thus, for example, under these conditions ββ-dimethyl adipic acid yields dimethyl-1.1-cyclopentanone-4,

and $\beta\beta$-dimethyl pimelic acid yields dimethyl-1.1-cyclo-hexanone-5.

$$(CH_3)_2.C.CH_2.COOH \qquad (CH_3)_2.C—CH_2.CO \qquad (CH_3)_2.C—CH_2$$
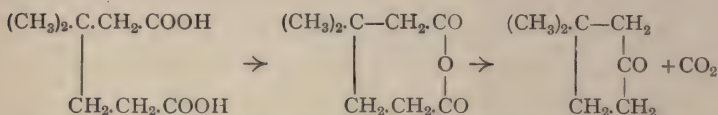
In connection with these cyclic ketones, Wallach has made the interesting observation that the oximes of the saturated members of the series are readily converted into iso-oximes by a Beckmann transformation, and these latter, on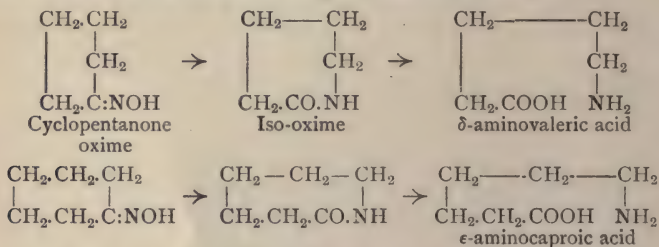 treatment with hydrochloric acid, then yield amino-acids, thus from cyclopentanone oxime, δ-aminovaleric acid is formed, whilst cyclohexanone oxime in the similar manner is converted into ε-aminocaproic acid, the mechanism of the reaction being represented thus :—

These acids may be (by the action of sodium nitrite on their hydrochlorides) transformed into unsaturated acids, in which the double bond is furthest removed from the carboxyl group, thus ε-aminocaproic acid under these conditions will yield hexene-5-acid.

$$HOOC.(CH_2)_3.CH_2.CH_2.NH_2 + HONO =$$
$$2H_2O + N_2 + HOOC.(CH_2)_3.CH:CH_2.$$
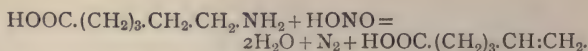
A similar series of transformations is obtained in the case of the complex cyclic ketones of the terpene series.

In the course of further observations on the cyclic ketones, Wallach has also shown that they condense quite readily with the Grignard reagent to form tertiary alcohols, which readily split out a molecule of water and form unsaturated hydrocarbons, containing the double linkage in the cyclic nucleus, thus :—

$$\begin{array}{ccc}
\overset{\displaystyle\text{---CH}_2}{\underset{\displaystyle\text{---CH}_2}{(\text{CH}_2)_n \quad \text{CO}}} & \xrightarrow{\;\text{RM}_g\text{X}\;} & \overset{\displaystyle\text{---CH}_2}{\underset{\displaystyle\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C(OH)}.\text{R}}} \rightarrow \overset{\displaystyle\text{---CH}_2}{\underset{\displaystyle\text{---CH}}{(\text{CH}_2)_n \quad \text{C.R}}}
\end{array}$$
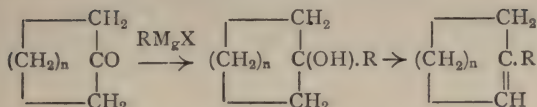
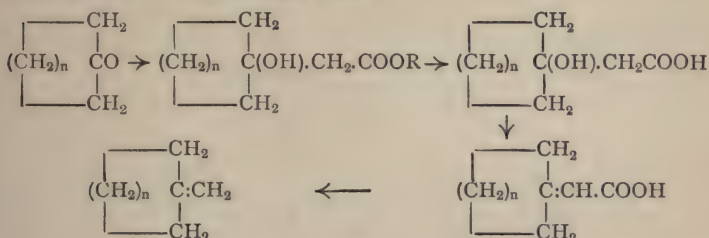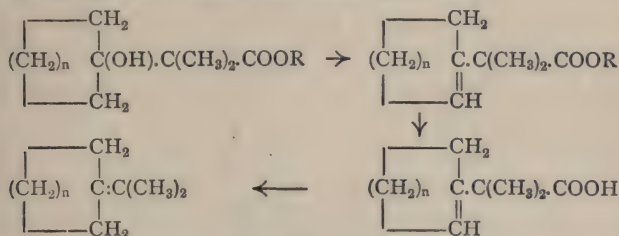If, however, the conditions be somewhat modified, and the ketone be condensed with the ethyl ester of bromacetic acid and zinc, and the resulting hydroxy-cyclo carboxylic acid be then heated with potassium bisulphate, an unsaturated acid is produced which on distillation yields an unsaturated hydrocarbon containing a semicyclic ethylenic linkage, thus :—
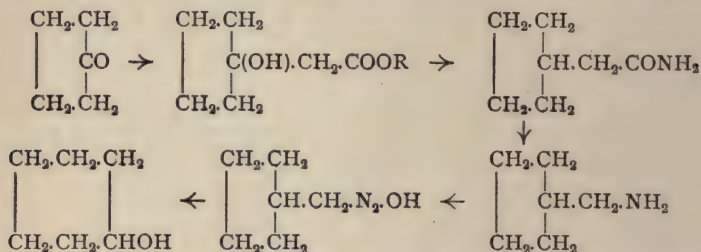
$$\begin{array}{ccc}
\overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{CO}}} \rightarrow \overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C(OH)}.\text{CH}_2.\text{COOR}}} & \rightarrow & \overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C(OH)}.\text{CH}_2\text{COOH}}} \\
& & \downarrow \\
\overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C:CH}_2}} & \longleftarrow & \overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C:CH.COOH}}}
\end{array}$$

An interesting case occurs if the ethyl ester of α-bromoisobutyric acid be used instead of the bromacetic ester, for the hydroxy ester produced can only give a cyclic unsaturated ester by loss of water, but if this ester be hydrolyzed, and the resulting acid be then distilled, a wandering of the ethylenic linkage takes place and a semicyclic ethylenic compound is formed.

$$\begin{array}{ccc}
\overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C(OH)}.\text{C(CH}_3)_2.\text{COOR}}} & \rightarrow & \overset{\text{---CH}_2}{\underset{\text{---CH}}{(\text{CH}_2)_n \quad \text{C.C(CH}_3)_2.\text{COOR}}} \\
& & \downarrow \\
\overset{\text{---CH}_2}{\underset{\text{---CH}_2}{(\text{CH}_2)_n \quad \text{C:C(CH}_3)_2}} & \longleftarrow & \overset{\text{---CH}_2}{\underset{\text{---CH}}{(\text{CH}_2)_n \quad \text{C.C(CH}_3)_2.\text{COOH}}}
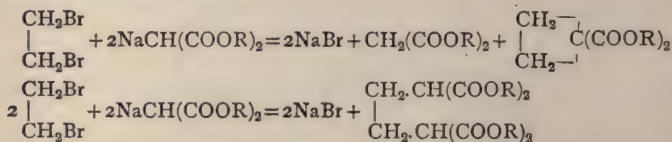\end{array}$$

Wallach has further shown (1907) that in the series of cyclic ketones it is possible to pass from one series to another (*e.g.* from cyclopentanone to cyclohexanone, etc.) by the following process. The cyclic ketones condense with bromo-acetic ester to give
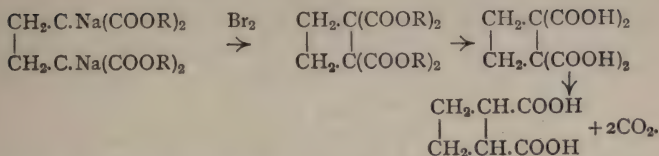
hydroxy esters, from which, by the action of hydrobromic acid and then reduction, the cyclic derivatives of acetic acid are formed. These acids may be converted into the corresponding amines by the Hofmann reaction, and from the nitrites of these amines, by the action of acids, products are obtained from which on boiling, nitrogen is eliminated, and the resulting compound, when hydrolyzed, yields an alcohol of the next higher system, which may be oxidized in the usual manner to a ketone, thus:—

$$
\begin{array}{ccc}
CH_2.CH_2 & CH_2.CH_2 & CH_2.CH_2 \\
\quad\bigg|\quad CO \rightarrow & \quad\bigg|\quad C(OH).CH_2.COOR \rightarrow & \quad\bigg|\quad CH.CH_2.CONH_2 \\
CH_2.CH_2 & CH_2.CH_2 & CH_2.CH_2 \\
& & \downarrow \\
CH_2.CH_2.CH_2 & CH_2.CH_2 & CH_2.CH_2 \\
\quad\bigg|\qquad\bigg|\quad \leftarrow & \quad\bigg|\quad CH.CH_2.N_2.OH \leftarrow & \quad\bigg|\quad CH.CH_2.NH_2 \\
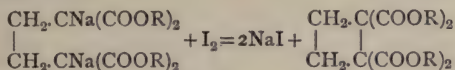CH_2.CH_2.CHOH & CH_2.CH_2 & CH_2.CH_2
\end{array}
$$

In the formation of acids and their esters we are chiefly indebted to the brilliant researches of W. H. Perkin, junr., who showed that the dihalogen paraffins condense readily with sodio-malonic ester or sodio-aceto-acetic ester to give esters of acids of the polymethylenes. The first reaction examined by Perkin was the condensation of ethylene dibromide with the ester, and here it was found that the reaction proceeded in two directions, one leading to the formation of an ester of tri-methylene dicarboxylic acid and the other to tetraethyl butane tetracarboxylate, thus:—

$$
\begin{array}{l}
CH_2Br \\
\quad\bigg|\quad +2NaCH(COOR)_2 = 2NaBr + CH_2(COOR)_2 + \begin{array}{l} CH_2- \\ \quad\bigg|\quad C(COOR)_2 \\ CH_2- \end{array} \\
CH_2Br
\end{array}
$$

$$
\begin{array}{l}
\quad CH_2Br \\
2\bigg|\quad +2NaCH(COOR)_2 = 2NaBr + \begin{array}{l} CH_2.CH(COOR)_2 \\ CH_2.CH(COOR)_2 \end{array} \\
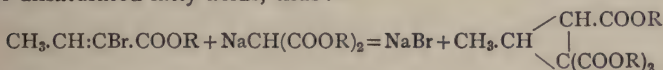\quad CH_2Br
\end{array}
$$

In the case of the second reaction, the resulting compound may be converted into a tetramethylene derivative by the action of bromine on its disodio-derivative, the resulting ester on hydrolysis yielding a tetracarboxylic acid which, when heated, loses carbon dioxide and yields tetramethylene dicarboxylic acid.

$$\begin{array}{cc} CH_2.C.Na(COOR)_2 \\ | \\ CH_2.C.Na(COOR)_2 \end{array} \xrightarrow{Br_2} \begin{array}{cc} CH_2.C(COOR)_2 \\ | \\ CH_2.C(COOR)_2 \end{array} \rightarrow \begin{array}{cc} CH_2.C(COOH)_2 \\ | \\ CH_2.C(COOH)_2 \end{array}$$

$$\downarrow$$

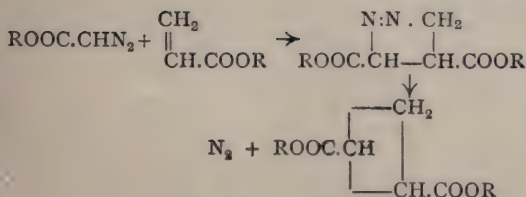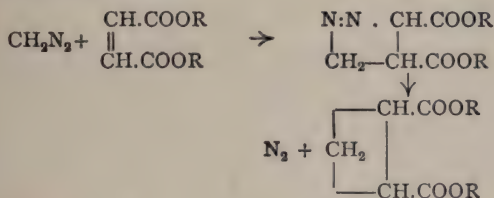$$\begin{array}{cc} CH_2.CH.COOH \\ | \\ CH_2.CH.COOH \end{array} + 2CO_2.$$

Again, Perkin has shown that by the action of halogens (preferably iodine) on the disodio derivatives of various esters (*e.g.* tetraethyl butane carboxylate), the esters of polymethylene acids are obtained.

$$\begin{array}{cc} CH_2.CNa(COOR)_2 \\ | \\ CH_2.CNa(COOR)_2 \end{array} + I_2 = 2NaI + \begin{array}{cc} CH_2.C(COOR)_2 \\ | \\ CH_2.C(COOR)_2 \end{array}$$

Other methods of preparation of acids of the trimethylene series have been worked out by Michael, who has shown that sodiomalonic ester condenses readily with α-halogen derivatives of unsaturated fatty acids, thus :—

$$CH_3.CH:CBr.COOR + NaCH(COOR)_2 = NaBr + CH_3.CH \begin{array}{c} \diagup CH.COOR \\ | \\ \diagdown C(COOR)_2 \end{array}$$

and by Buchner, who, by the condensation of diazomethane or diazoacetic ester with the esters of unsaturated acids, obtained pyrazoline carboxylic acids which, on heating, decompose with evolution of nitrogen, and the consequent formation of acids of the trimethylene series.

$$CH_2N_2 + \begin{array}{c} CH.COOR \\ || \\ CH.COOR \end{array} \rightarrow \begin{array}{c} N:N \ . \ CH.COOR \\ | \quad | \\ CH_2 - CH.COOR \end{array}$$

$$\downarrow$$

$$N_2 + \begin{array}{c} \overline{}CH.COOR \\ CH_2 \quad | \\ \underline{}CH.COOR \end{array}$$

$$ROOC.CHN_2 + \begin{array}{c} CH_2 \\ || \\ CH.COOR \end{array} \rightarrow \begin{array}{c} N:N \ . \ CH_2 \\ | \quad | \\ ROOC.CH - CH.COOR \end{array}$$

$$\downarrow$$

$$N_2 + \begin{array}{c} \overline{}CH_2 \\ ROOC.CH \quad | \\ \underline{}CH.COOR \end{array}$$

In the hexamethylene series Zelinsky has shown that the Grignard reaction is applicable for the preparation of acids when the monobromo, or monoiodo substitution derivatives of the hydrocarbons are used. These halogen derivatives are brought into contact with magnesium in the usual way in ether solution and the resulting magnesium iodide or chloride on treatment with dry carbon dioxide and subsequent decomposition with dilute sulphuric acid yields the hexamethylene carboxylic acid

$$C_6H_{11}I \rightarrow C_6H_{11}MgI \rightarrow C_6H_{11}.COOMgI \rightarrow C_6H_{11}.COOH.$$
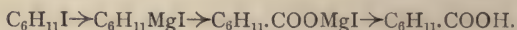
In the polymethylene compounds no cases of isomerism are met with in the monosubstituted derivatives, but in the di- and poly-substituted derivatives isomerism due to the position of the substituent in the molecule is possible, thus in the tetramethylene series the following dicarboxylic acids are possible:—

1. $(HOOC)_2.C—CH_2$ 1. $HOOC.CH. CH.COOH$ 2.
     $CH_2.CH_2.$ $CH_2.CH_2$

1. $HOOC.CH . CH_2$
     $CH_2.CH.COOH$ 3,
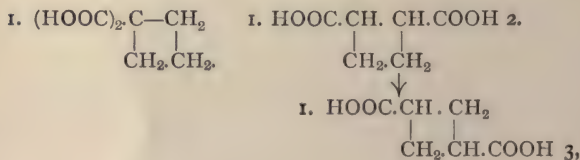
namely, the 1.1, 1.2 and 1.3 acids, the carboxyl groups occupying the positions shown. Again, some disubstituted derivatives are found to exist in stereo-isomeric forms, due to the spatial configuration of the molecule, thus in the case of the tetramethylene -1.2-dicarboxylic acid two forms are known, namely, the *cis*-acid, which melts at 137-138° C., and the *trans*-acid, which melts at 131° C. This isomerism can be accounted for in the following manner by considering that the plane of the paper represents the plane in which the carbon atoms of the ring lie, when the carboxyl groups may be considered as both being in the same plane either above or below the plane of the paper, or one may be in the plane above that of the paper and one in the plane below that of

the paper. This explanation leads to the following pictorial representation of the acids :—
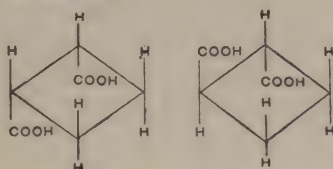

The former is known as the *cis*-acid, the latter as the *trans*-acid. A very neat method of representing these cases of isomerism has been devised by *Aschan*, who represents the plane of the carbon atoms of the ring as a straight line, and denotes the substituted hydrogen atoms by the letters X, Y, Z. Thus, for the dicarboxylic acids of the trimethylene series, if the carboxyl groups are represented by X, we have the following possibilities—
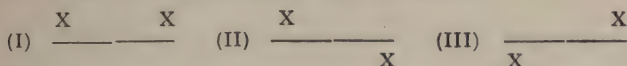
where (I) would represent the internally compensated active form of the acid, whilst (II) and (III), which are mirror images, represent the active forms of the acids. The configuration (I) is that of the *cis*-acid, (II) being that of the *trans*-acid, and since the artificially prepared *trans*-acids are optically inactive it is probable that they consist of racemic mixtures of (II) and (III).

In dealing with the various groups, only those compounds will be mentioned which possess an historical interest, or which are of importance as decomposition products of other series.

Cyclopropanes.—Of this series, cyclopropane itself and caronic acid are perhaps the most important members. The hydrocarbon was obtained by Freund in 1882, and was the first synthetic cyclic hydrocarbon to be prepared, containing less than six atoms of carbon. It was prepared by heating trimethylene bromide with sodium, the reaction taking place as follows :—
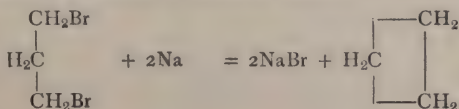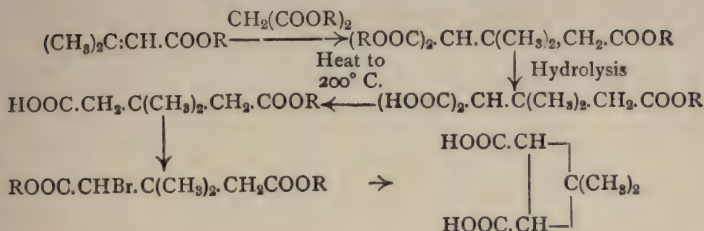
At ordinary temperature and pressure it is a gas which shows a marked difference in chemical behaviour from the isomeric propylene, for whereas the latter rapidly absorbs bromine with formation of propylene dibromide $CH_3.CHBr.CH_2Br$, cyclopropane is attacked very slowly and then yields trimethylene bromide. Again, hydriodic acid reacts with cyclopropane to form normal propyl iodide, whilst propylene, under similar conditions, yields isopropyl iodide. These reactions necessarily point to a difference in structure between cyclopropane and propylene, and are best explained by giving to the former the cyclic grouping of the carbon atoms.

Caronic acid $(CH_3)_2.C_3H_2.(COOH)_2$ is a dimethyl cyclopropane dicarboxylic acid, which was first obtained by Baeyer from the oxidation of carone with a warm solution of potassium permanganate. From the fact that hydrobromic acid converts caronic acid into the isomeric terebic acid, Baeyer considered that caronic acid must be a *gem*-dimethyl cyclopropane dicarboxylic acid,[1] the reactions above mentioned proceeding as follows :—
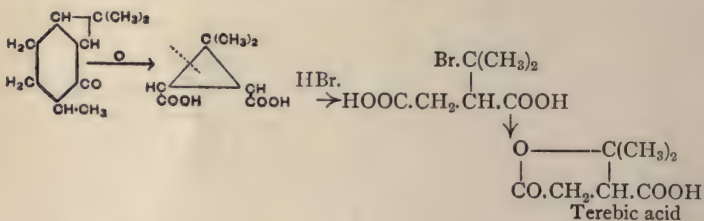
This structure for caronic acid was afterwards confirmed by W. H. Perkin, jun., and Thorpe, who showed that the ethyl ester of dimethylacrylic acid condenses with ethyl malonate to form ethyl dimethyl propane tricarboxylic ester. This ester when hydrolyzed yields the free acid, which, when heated, is converted into $\beta\beta$-dimethyl glutaric acid. The α-bromodimethyl ester of the latter acid, when warmed with alcoholic potash, is converted into a mixture of *cis*- and *trans*-caronic acid.

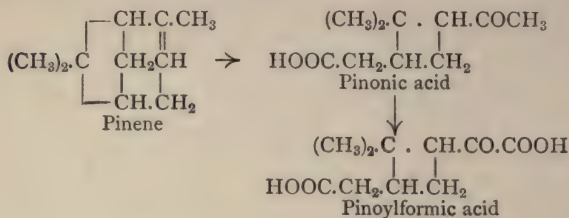[1] The prefix "*gem*" is used to denote that two alkyl groups are attached to the same carbon atom.

$$CH_2(COOR)_2$$
$$(CH_3)_2C:CH.COOR \xrightarrow{} (ROOC)_2.CH.C(CH_3)_2.CH_2.COOR$$
$$\text{Heat to} \qquad \downarrow \text{Hydrolysis}$$
$$200° C.$$
$$HOOC.CH_2.C(CH_3)_2.CH_2.COOR \longleftarrow (HOOC)_2.CH.C(CH_3)_2.CH_2.COOR$$

$$\downarrow \qquad\qquad\qquad HOOC.CH—$$

$$ROOC.CHBr.C(CH_3)_2.CH_2COOR \quad \rightarrow \quad \Big| \quad C(CH_3)_2$$

$$HOOC.CH—$$

The two forms of the acid may be separated by means of their ammonium salts, that of the *cis*-form being much more soluble in hot alcohol than the corresponding salt of the *trans*-acid.
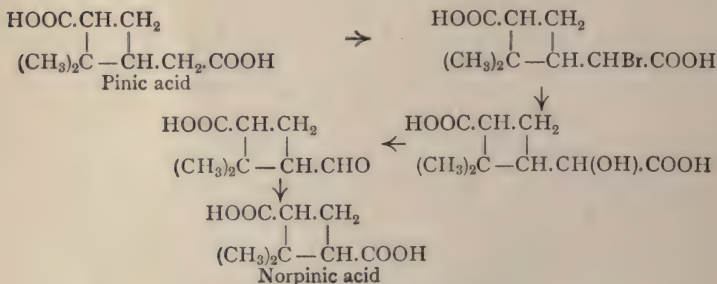
Cyclobutanes.—Many attempts were made by the earlier investigators to isolate the parent hydrocarbon of this group, all of which were unsuccessful until Willstätter, in 1907, showed that the unsaturated cyclobutene was capable of reduction by the Sabatier and Senderens method at comparatively low temperature. The hydrocarbon is a very volatile liquid, the vapour of which burns with a luminous flame. On further reduction by the above method at a temperature of 180-200° C. it yields *n*-butane. The cyclobutene required for the above reaction is produced by the distillation of trimethylcyclobutylammonium hydroxide (which is obtained by methylating cyclobutylamine in the usual manner), the process thus being an adaptation of Hofmann's "destructive methylation process" (see Alkaloids).

Among the other compounds belonging to this series may be mentioned *pinonic acid*, $C_{10}H_{16}O_3$, and *pinoylformic acid*, $C_{10}H_{14}O_5$, which are obtained when pinene, is oxidized with potassium permanganate at low temperature, the former acid being the chief product of the action, the latter being obtained in the form of its bisulphite compound from the mother liquor remaining after crystallization of the pinonic acid. Assuming Wagner's formula for pinene, the formation of pinonic acid and pinoylformic acid may be represented thus :—
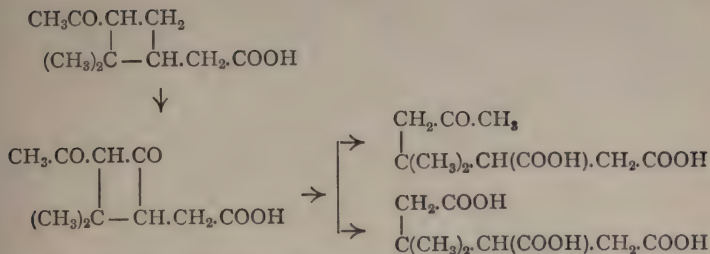
$$
\begin{array}{cc}
\overset{\displaystyle -CH.C.CH_3}{\underset{\displaystyle -CH.CH_2}{(CH_3)_2.C \quad CH_2CH}} & (CH_3)_2.C \cdot CH.COCH_3 \\
& \rightarrow \quad HOOC.CH_2.CH.CH_2 \\
\text{Pinene} & \text{Pinonic acid}
\end{array}
$$

$$
\begin{array}{c}
(CH_3)_2.C \cdot CH.CO.COOH \\
HOOC.CH_2.CH.CH_2 \\
\text{Pinoylformic acid}
\end{array}
$$
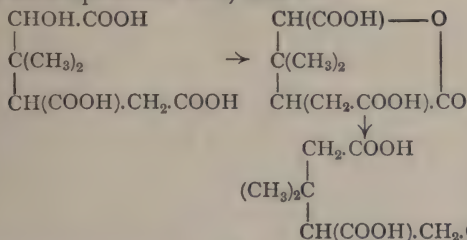
By oxidation of pinonic acid with sodium hypobromite *pinic acid* $C_9H_{14}O_4$ is obtained, the grouping $-CH.CO.CH_3$ being transformed into $-CH.COOH$, with elimination of bromoform. This acid readily forms a bromo-derivative which, by the action of caustic baryta, passes into the corresponding hydroxyl derivative. The latter compound on boiling its acqueous solution with lead peroxide is oxidized to an aldehyde acid, which, on further oxidation with potassium permanganate, is transformed into *norpinic acid* $C_8H_{12}O_4$, thus :—

$$
\begin{array}{ccc}
\overset{\displaystyle HOOC.CH.CH_2}{(CH_3)_2C - CH.CH_2.COOH} & \rightarrow & \overset{\displaystyle HOOC.CH.CH_2}{(CH_3)_2C - CH.CHBr.COOH} \\
\text{Pinic acid} & &
\end{array}
$$

$$
\begin{array}{ccc}
\overset{\displaystyle HOOC.CH.CH_2}{(CH_3)_2C - CH.CHO} & \leftarrow & \overset{\displaystyle HOOC.CH.CH_2}{(CH_3)_2C - CH.CH(OH).COOH}
\end{array}
$$

$$
\begin{array}{c}
HOOC.CH.CH_2 \\
(CH_3)_2C - CH.COOH \\
\text{Norpinic acid}
\end{array}
$$

By the oxidation of pinonic acid with chromic acid mixture the tetramethylene ring is broken and two acids, namely, *isoketocamphoric acid*, $C_{10}H_{16}O_5$ and *isocamphoronic acid*, $C_9H_{14}O_6$, are obtained. Such an oxidation may be explained by the following scheme :—

$$\begin{array}{l} CH_3CO.CH.CH_2 \\ \quad\ \ | \qquad\ | \\ (CH_3)_2C - CH.CH_2.COOH \end{array}$$

$$\downarrow$$

$$\begin{array}{l} CH_3.CO.CH.CO \\ \quad\ \ \ | \qquad\ | \\ (CH_3)_2C - CH.CH_2.COOH \end{array} \rightarrow \left[\begin{array}{l} \rightarrow \begin{array}{l} CH_2.CO.CH_3 \\ | \\ C(CH_3)_2.CH(COOH).CH_2.COOH \end{array} \\ \rightarrow \begin{array}{l} CH_2.COOH \\ | \\ C(CH_3)_2.CH(COOH).CH_2.COOH \end{array} \end{array} \right.$$

In a similar manner pinoylformic acid on oxidation with bleaching powder is converted into *ketoisocamphoronic acid* $HOOC.CO.C(CH_3)_2.CH(COOH).CH_2.COOH$, which on reduction with sodium amalgam gives the lactone of α-hydroxyisocamphoronic acid, and the latter on reduction gives a quantitative yield of isocamphoronic acid, thus :—
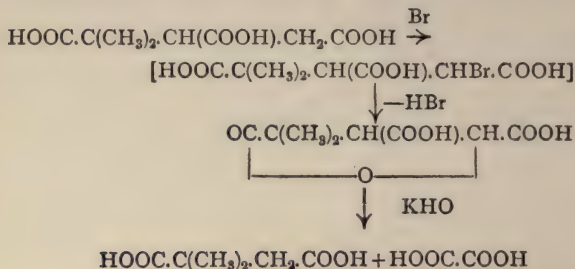
$$\begin{array}{l} CHOH.COOH \\ | \\ C(CH_3)_2 \\ | \\ CH(COOH).CH_2.COOH \end{array} \rightarrow \begin{array}{l} CH(COOH) \!-\!\!-\! O \\ | \qquad\qquad\ | \\ C(CH_3)_2 \qquad\ | \\ | \qquad\qquad\ | \\ CH(CH_2.COOH).CO \end{array}$$

$$\downarrow$$

$$\begin{array}{l} CH_2.COOH \\ | \\ (CH_3)_2C \\ | \\ CH(COOH).CH_2.COOH \end{array}$$

The ketoisocamphoronic acid obtained above when oxidized with lead peroxide yields the dimethyltricarballylic acid $C_8H_{12}O_6$, which was obtained by Tiemann and Semmler from the action of a concentrated alkaline solution of potassium permanganate on pinonic acid.

$$HOOC.CO.C(CH_3)_2.CH(COOH).CH_2.COOH \overset{O}{\rightarrow}$$
$$HOOC.C(CH_3)_2.CH.(COOH).CH_2(COOH).$$
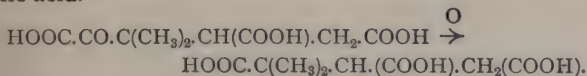
The determination of the constitution of this dimethyltricarballylic acid is of fundamental importance since the formulation of pinonic acid and its derivatives depend entirely upon it. It was settled by A. v. Baeyer, who heated the acid with phosphorus tribromide and bromine, and then fused the resulting lactonic acid with caustic potash, when oxalic acid and asymmetrical dimethyl-succinic acid were obtained.

$$\text{HOOC.C(CH}_3)_2\text{.CH(COOH).CH}_2\text{.COOH} \xrightarrow{\text{Br}}$$

$$[\text{HOOC.C(CH}_3)_2\text{.CH(COOH).CHBr.COOH}]$$

$$\downarrow -\text{HBr}$$

$$\text{OC.C(CH}_3)_2\text{.CH(COOH).CH.COOH}$$

$$\underline{\qquad\qquad\text{O}\qquad\qquad}$$

$$\downarrow \text{ KHO}$$

$$\text{HOOC.C(CH}_3)_2\text{.CH}_2\text{.COOH} + \text{HOOC.COOH}$$

It was also ascertained that the dimethyltricarballylic acid contained no malonic acid grouping, and consequently the formula given above must be correct. Thus dimethyltricarballylic acid, isocamphoronic acid, and ketoisocamphoronic acid contain two methyl groups linked to one and the same carbon atom, from which it follows that the pinic acid series contains the same grouping.

The truxillic acids $C_{18}H_{16}O_4$, which are derived from the alkaloid truxilline, are diphenylcyclobutane dicarboxylic acids. They are formed when truxilline is boiled with hydrochloric acid, the alkaloid breaking down into ecgonine, methyl alcohol, and truxillic acid.

$$C_{38}H_{46}N_2O_8 + 4H_2O = C_{18}H_{16}O_4 + 2CH_3OH + 2C_9H_{15}NO_3.$$
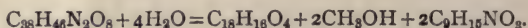
Their constitution was determined by Liebermann, who showed that they are polymers of cinnamic acid, into which they readily pass on distillation. They are stable towards potassium permanganate. The α- and β-truxillic acids, which are simultaneously formed in the hydrolysis of truxilline, are separated by means of their barium salts, that of the α-acid being soluble in water and that of the β-acid being insoluble. The α-acid has been snythesized by the oxidation of diphenyl-2.4-cyclobutane-bis-methylene malonic acid with potassium permanganate, the latter acid resulting when cinnamic aldehyde, malonic acid, and quinoline are left in contact for some days.
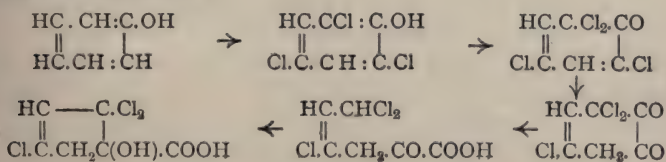
$$C_6H_5CH:CH.CHO + H_2C.(COOH)_2 = C_6H_5CH:CH.CH:C(COOH)_2$$

$$2C_6H_5.CH:CH.CH:C(COOH)_2 = \begin{matrix} C_6H_5.CH.CH.CH:C(COOH)_2 \\ | \quad | \\ (HOOC)_2C:CH.CH.CH.C_6H_5 \end{matrix}$$

$$\downarrow O$$

$$\begin{matrix} C_6H_5.CH.CH.COOH \\ | \quad | \\ HOOC.CH.CH.C_6H_5 \end{matrix}$$
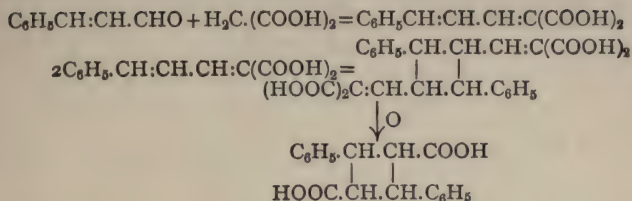
This acid yields an anhydride when its sodium salt is heated with a solution of its acid chloride in benzene, but if the free α-acid is heated with acetic anhydride it is transformed into the anhydride of the stereo-isomeric γ-truxillic acid. β-truxillic acid is most probably a diphenyl-3.4-cyclobutane-dicarboxylic acid-1.2,

$$\begin{matrix} 2. \; HOOC.CH—CH.C_6H_5 \; 3. \\ | \quad | \\ 1. \; HOOC.CH—CH.C_6H_5 \; 4. \end{matrix}$$
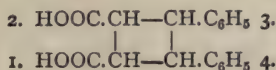
since on oxidation with potassium permanganate it gives benzoic acid and benzil, $C_6H_5CO.CO.C_6H_5$, which naturally points to the presence of the grouping $C_6H_5.C - C.C_6H_5$ in the molecule. When fused with caustic alkali, it passes into the stereo-isomeric δ-truxillic acid.

Cyclopentanes.—In this group of cyclic compounds one has, in addition to the ordinary means of preparation, an extremely novel method due chiefly to the investigations of Zincke and also of Hantzsch, which consists in the simultaneous chlorination and oxidation of phenols. For example, phenol in alkaline solution, when acted upon by chlorine, forms a trichlorophenol which is converted by hypochlorous acid into a trichlorodiketocyclo-hexene. In the presence of alkali this compound decomposes with the intermediate rupture of the cyclohexene ring, and the keto-acid formed undergoes rearrangement, yielding a cyclo-pentane derivative—
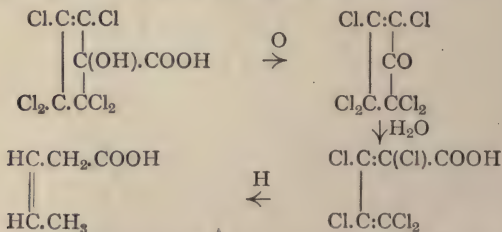
$$\begin{matrix} HC.CH:C.OH \\ \| \quad | \\ HC.CH:CH \end{matrix} \rightarrow \begin{matrix} HC.CCl:C.OH \\ \| \quad | \\ Cl.C.CH:C.Cl \end{matrix} \rightarrow \begin{matrix} HC.C.Cl_2.CO \\ \| \quad | \\ Cl.C.CH:C.Cl \end{matrix}$$

$$\begin{matrix} HC——C.Cl_2 \\ \| \quad | \\ Cl.C.CH_2C(OH).COOH \end{matrix} \leftarrow \begin{matrix} HC.CHCl_2 \\ \| \quad | \\ Cl.C.CH_2.CO.COOH \end{matrix} \leftarrow \begin{matrix} HC.CCl_2.CO \\ \| \quad | \\ Cl.C.CH_2.CO \end{matrix}$$
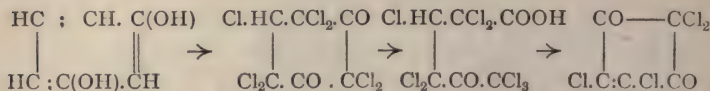
2

Catechol similarly on chlorination yields a tetrachloro-ortho-benzoquinone, which on further chlorination forms a hexachloro-derivative from which, by warming with water, a hydroxy-cyclo-pentane carboxylic acid is obtained.
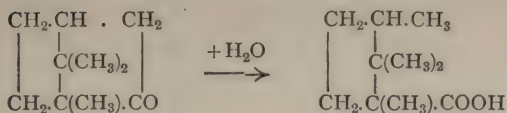
$$
\begin{array}{cccc}
\text{HC:CH.C.OH} & \text{Cl.C:CCl.CO} & \text{Cl.C:C.Cl.CO} & \text{Cl.C:C.Cl} \\
\quad\big\| \quad\rightarrow & \quad\big| \quad\rightarrow & \quad\big| \quad\rightarrow & \big| \\
\text{HC:CH.C.OH} & \text{Cl.C:C.Cl.CO} & \text{Cl}_2\text{C.C.Cl}_2\text{.CO} & \text{Cl}_2\text{C.C.Cl}
\end{array}
$$

with the final structure bearing C(OH).COOH
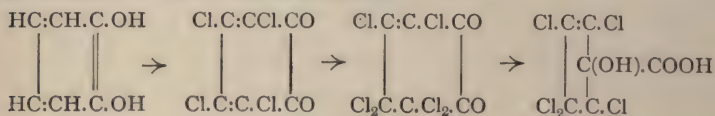
That the acid formed possesses this constitution is shown by the facts that on oxidation it yields a ketone which, by the action of alkalies, is converted into perchlorovinylacrylic acid, from which ethylidene propionic acid is obtained by reduction.

$$
\begin{array}{ccc}
\text{Cl.C:C.Cl} & \overset{O}{\rightarrow} & \text{Cl.C:C.Cl} \\
\big| \text{C(OH).COOH} & & \big| \text{CO} \\
\text{Cl}_2\text{.C.CCl}_2 & & \text{Cl}_2\text{C.CCl}_2 \\
& & \downarrow \text{H}_2\text{O} \\
\text{HC.CH}_2\text{.COOH} & \overset{H}{\leftarrow} & \text{Cl.C:C(Cl).COOH} \\
\big\| & & \big| \\
\text{HC.CH}_3 & & \text{Cl.C:CCl}_2
\end{array}
$$

In the same way resorcinol, when chlorinated in glacial acetic acid solution, forms a heptachlororesorcinol, which on treatment with chlorine and water is transformed into trichloro-acetyl penta-chlorobutyric acid. The latter acid when boiled with water is decomposed with elimination of hydrochloric acid and carbon dioxide, and consequent formation of a tetrachloro-diketo cyclo-pentene.

$$
\begin{array}{cccc}
\text{HC : CH. C(OH)} & \text{Cl.HC.CCl}_2\text{.CO} & \text{Cl.HC.CCl}_2\text{.COOH} & \text{CO——CCl}_2 \\
\big| \quad\rightarrow & \big| \quad\rightarrow & \big| \quad\rightarrow & \big| \\
\text{HC : C(OH).CH} & \text{Cl}_2\text{C. CO . CCl}_2 & \text{Cl}_2\text{C.CO.CCl}_3 & \text{Cl.C:C.Cl.CO}
\end{array}
$$

Many of the decomposition products of the camphor compounds are derivatives of the cyclopentane series, and as such will be considered in the following pages. Campholic acid, $C_{10}H_{18}O_2$, is a tetramethyl cyclopentane carboxylic acid, which is formed by the prolonged heating of a solution of camphor in xylene, with sodium, or by the action of bases with camphor.
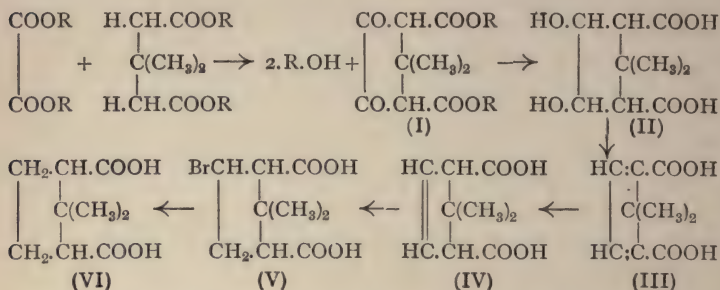
$$\begin{array}{ccc}
\text{CH}_2.\text{CH . CH}_2 & & \text{CH}_2.\text{CH.CH}_3 \\
\Big| \quad \underset{|}{\text{C}(\text{CH}_3)_2} \quad \Big| & \xrightarrow{+\ \text{H}_2\text{O}} & \Big| \quad \underset{|}{\text{C}(\text{CH}_3)_2} \quad \Big| \\
\text{CH}_2.\text{C}(\text{CH}_3).\text{CO} & & \text{CH}_2.\text{C}(\text{CH}_3).\text{COOH}
\end{array}$$

This structure of the acid is confirmed by the synthesis of the acid by Haller and Blanc in 1900 from campholid, which readily adds on the elements of hydrobromic acid, yielding a bromo-campholic acid which on reduction is transformed into campholic acid.

$$\begin{array}{ccccc}
\underset{\text{C}_8\text{H}_{14}}{\boxed{}}\begin{matrix}\text{---CH}_2 \\ \text{O} \\ \text{---CO}\end{matrix} & \rightarrow & \underset{\text{C}_8\text{H}_{14}}{\begin{matrix}\text{CH}_2\text{Br} \\ | \\ \text{COOH}\end{matrix}} & \rightarrow & \underset{\text{C}_8\text{H}_{14}}{\begin{matrix}\text{CH}_3 \\ | \\ \text{COOH}\end{matrix}}
\end{array}$$
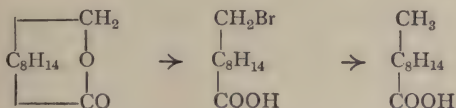
Nitric acid oxidizes it readily to camphoric acid, $C_8H_{14}(COOH)_2$, and to camphoronic acid, $C_6H_{11}(COOH)_3$, whilst when heated with soda lime it is converted into the unsaturated hydrocarbon campholene.

Apocamphoric acid, $C_8H_{14}O_4$, is a lower homologue of camphoric acid and was first obtained by Marsh and Gardner by the elimination of carbon dioxide from the camphoric acid ($C_9H_{14}O_6$) which they obtained from the action of nitric acid on camphene. It is also produced in the oxidation of bornyl chloride with nitric acid, and its constitution has been definitely determined by its synthesis in 1901 by Komppa. In this synthesis the dimethyl ester of $\beta\beta$-dimethyl glutaric acid is condensed with oxalic ester in the presence of sodium ethoxide to form diketoapocamphoric ester (I), which on reduction yields the corresponding dihydroxyapo-camphoric acid (II). The latter acid, when heated for some time with hydriodic acid and red phosphorus, yields an unsaturated acid (III). This acid, on further reduction with sodium and amyl alcohol, is transformed into another unsaturated acid the constitution of which is most probably to be represented by the formula (IV). On heating this acid with hydrobromic acid and glacial acetic acid, a saturated bromo-compound (V) is obtained, from which by reduction with zinc dust and acetic acid, apo-camphoric acid (VI) finally results.

$$\begin{array}{ccccc}
\text{COOR} & \text{H.CH.COOR} & & \text{CO.CH.COOR} & \text{HO.CH.CH.COOH} \\
| & | & & | & | \\
| \quad + & \text{C(CH}_3)_2 \longrightarrow 2.\text{R.OH} + & \text{C(CH}_3)_2 & \longrightarrow & \text{C(CH}_3)_2 \\
| & | & & | & | \\
\text{COOR} & \text{H.CH.COOR} & & \text{CO.CH.COOR} & \text{HO.CH.CH.COOH} \\
& & & \text{(I)} & \quad\quad \downarrow \text{ (II)}
\end{array}$$

$$\begin{array}{cccc}
\text{CH}_2.\text{CH.COOH} & \text{BrCH.CH.COOH} & \text{HC.CH.COOH} & \text{HC:C.COOH} \\
| & | & \| \; | & \| \; | \\
\text{C(CH}_3)_2 \longleftarrow & \text{C(CH}_3)_2 \longleftarrow & \text{C(CH}_3)_2 \longleftarrow & \text{C(CH}_3)_2 \\
| & | & \| \; | & \| \; | \\
\text{CH}_2.\text{CH.COOH} & \text{CH}_2.\text{CH.COOH} & \text{HC.CH.COOH} & \text{HC:C.COOH} \\
\text{(VI)} & \text{(V)} & \text{(IV)} & \text{(III)}
\end{array}$$

The acid on treatment with acetyl chloride and alkali is decomposed into its two stereoisomeric components, the *cis*-acid being transformed into its anhydride, which can be separated from the unaltered *trans*-acid by shaking up with sodium carbonate solution.

Camphoric acid, $C_{10}H_{16}O_4$, a trimethylcyclopentane dicarboxylic acid, is one of the longest known of the alicyclic compounds. It was apparently first obtained by Kosegarten in 1785, by the oxidation of camphor with nitric acid. The acid of above composition is found to exist in six different forms, namely, the *d*, *l*, and racemic forms, and the *d*, *l*, and racemic forms of the corresponding isocamphoric acid, the active varieties of which are prepared from *l* and *d*-camphoric acid respectively when these latter are heated for some time with acids or with water to high temperatures. The most important of these acids is the *d*-camphoric acid, obtained by the oxidation of camphor with nitric acid.

$$C_8H_{14}\begin{array}{|c} \overline{\quad\quad}\text{CH}_2 \\ \\ \underline{\quad\quad}\text{CO} \end{array} \longrightarrow \quad C_8H_{14}(\text{COOH})_2$$

It crystallizes in prisms (melting at 187° C.), and is converted into its anhydride by the action of acetyl chloride. It is readily oxidized by potassium permanganate, yielding oxalic acid and a diabasic acid, $C_8H_{12}O_5$ (known as Balbiano's acid), together with small quantities of camphanic, camphoronic, and trimethyl succinic acid. On reduction with hydriodic acid it yields $\alpha\beta\beta$-trimethyl glutaric acid, which points to the grouping HOOC.C$(CH_3).C(CH_3)_2.C.COOH$ in the molecule.

Owing to the unsymmetrical positions of the $-(COOH)$ groups in the molecule, two series of acid esters are known, one containing the grouping $-CH.COOR$, designated as *ortho*-esters, which result from the action of sodium alcoholates on camphoric anhydride or on heating the anhydride with alcohols, the other, containing the grouping $-C(CH_3)-COOR$, and known as *allo*-esters, which are produced when the neutral esters are heated for a short time with alcoholic potash. The constitution of camphoric acid has been definitely settled by its synthesis at the hands of Komppa in 1903,[1] although previously to this a general idea of its structure was known through the work of Bredt and others. The investigations of Bredt, based on the decomposition of camphoronic acid, led him to assign the formula (I) to camphor, from which it follows that camphoric acid must be represented by formula (II).

$$\text{(I)} \quad \begin{array}{c} CH_2.CH\text{------}CH_2 \\ | \qquad | \qquad | \\ C(CH_3)_2 \\ | \qquad\qquad | \\ CH_2.C(CH_3)\text{---}CO \end{array} \quad \xrightarrow{\;O\;} \quad \begin{array}{c} CH_2.CH.COOH \\ | \qquad\qquad \\ C(CH_3)_2 \\ | \qquad\qquad \\ CH_2.C(CH_3).COOH \end{array} \quad \text{(II)}$$
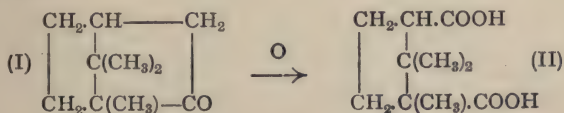
Further confirmation of the above-given structure is shown (*a*) by the formation of $\alpha\beta\beta$-trimethyl glutaric acid, $HOOC.CH(CH_3).C(CH_3)_2.CH_2.COOH$ (see above), and (*b*) that camphoric acid must be a substituted glutaric or adipic acid, and consequently its next higher homologue, homocamphoric acid, whose calcium salt yields camphor (a ring ketone) on distillation, must be either a substituted adipic or pimelic acid, since experience shows that only acids of these types give ring ketones on distillation of their salts. Again, since α-oxycamphoric acid readily lactonizes to form a γ-lactone (camphanic acid), it follows that a dibasic acid whose α-oxyderivative yields a γ-lactone must be a glutaric acid derivative. Further, camphoric acid contains a trimethyl cyclopentane ring, since Lapworth has shown that α-dibromocamphor is readily converted by silver nitrate into homocamphoronic acid, $C_7H_{13}(COOH)_3$, an open chain tribasic acid, the anhydride of which on heating is converted into cam-

[1] See footnote, p. 94.

phononic acid, $C_9H_{14}O_3$, a monobasic ketonic acid formed by the elimination of carbon dioxide from the anhydride, and consequent closing of the ring. On oxidation, camphononic acid yields camphoronic acid (*i.e.* $\alpha\alpha\beta$-trimethyl carballylic acid, $(CH_3)_2.C(COOH).(CH_3).C(COOH).CH_2.COOH.$), consequently camphononic acid must contain three methyl groups; and since another carbon atom is present as $-COOH$, this leaves a residue of five carbon atoms, one of which is present as a keto-group. These must represent a five-carbon ring nucleus, since the cyclic ketonic acid (camphononic acid) is obtained from the open chain tribasic acid (homocamphoronic acid), and the formation of ring ketones with less than five atoms of carbon has not as yet been observed. Homocamphoronic and camphononic acids must thus be—

$$
\begin{array}{ll}
\underbrace{
\begin{array}{l}
CH_2.COOH \\
| \\
C(CH_3)_2.COOH \quad\text{or} \\
| \\
CH_2.C(CH_3).COOH
\end{array}
\qquad
\begin{array}{l}
COOH \\
| \quad CH_2.COOH \\
C(CH_3)_2 \\
| \\
CH_2.C(CH_3).COOH
\end{array}
}
\end{array}
$$

Homocamphoronic acid

$$
\begin{array}{ll}
\underbrace{
\begin{array}{l}
CH_2.CO \\
| \\
\quad C(CH_3)_2 \qquad\text{or} \\
| \\
CH_2.C(CH_3).COOH
\end{array}
\qquad
\begin{array}{l}
CO.CH_2 \\
| \\
\quad C(CH_3)_2 \\
| \\
CH_2.C(CH_3).COOH
\end{array}
}
\end{array}
$$
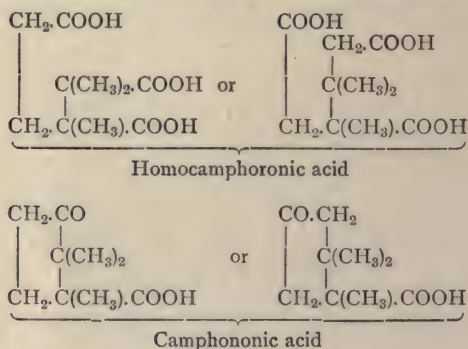
Camphononic acid

Again, homocamphoric acid on bromination yields an α-bromo-derivative from which, by removal of the elements of hydrobromic acid, dehydrohomocamphoric acid is obtained,

$$HOOC.(C_7H_{13}){:}CH.CH_2.COOH \rightarrow HOOC.(C_7H_{13}){:}CH.CHBr.COOH \rightarrow$$
$$HOOC(C_7H_{13}){:}C{:}CH.COOH\ ;$$
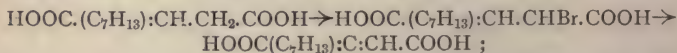
and since the oxidation of dehydrocamphoric acid yields camphononic acid, $HOOC(C_7H_{13}){:}CO$, it follows that homocamphoric acid and camphoric acid contain the same cyclic nucleus as camphononic acid.

A complete synthesis of camphoric acid was carried out in 1903 by Komppa, from diketoapocamphoric ester (see p. 20).

This was methylated in the ordinary manner, and from the mixture of reaction products a diketocamphoric ester (I) was isolated. On reduction with sodium amalgam this furnishes a dihydroxycamphoric acid (II), which by heating for some time with hydriodic acid and amorphous phosphorus, is transformed into the unsaturated racemic dehydrocamphoric acid (III). This acid readily combines with hydrobromic acid to form β-bromo-camphoric acid (IV), which on reduction with zinc dust and acetic acid yields mesocamphoric acid (V). The meso-acid was split by the action of acetyl chloride into the anhydride of a *cis*-acid, and a *trans*-acid which was not capable of yielding an anhydride. The *cis*-anhydride is identical with the anhydride of racemic camphoric acid, and the *trans*-acid is identical with racemic isocamphoric acid.

CO.CH.COOCH₃   CO.CH.COOCH₃   HO.CH.CH.COOH
    | | |
    C(CH₃)₂   →   C(CH₃)₂   →   C(CH₃)₂
    | | |
CO.CH.COOCH₃   CO.C(CH₃).COOCH₃   HO.CH.C(CH₃).COOH
                            (I)   (II)

CH₂.CH.COOH   BrCH.CH.COOH   CH:C.COOH
    | | |
    C(CH₃)₂   ←   C(CH₃)₂   ←   C(CH₃)₂
    | | |
CH₂.C(CH₃).COOH   CH₂.C(CH₃).COOH   CH₂.C(CH₃).COOH
    (V)   (IV)   (III)
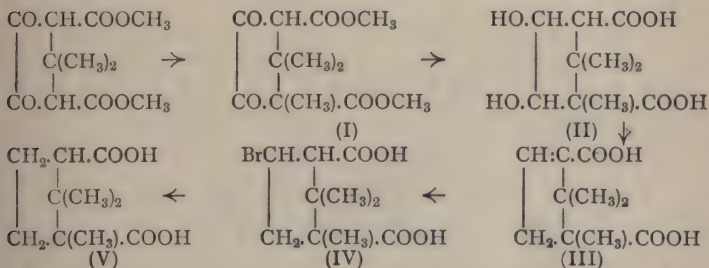
W. H. Perkin, junr., has recently (1906) synthesized camphoric acid starting from $\alpha\alpha$-dimethylbutane-$\alpha\beta\delta$-carboxylate, the sodium salt of which on treatment with acetic anhydride yields a dimethyl cyclopentanone carboxylic acid. The ester of this acid on treatment with magnesium methyl iodide is converted into α-campholactone. The latter compound by the action of fuming hydrobromic acid yields a bromotrimethyl cyclopentane carboxylic acid, which on shaking with potassium cyanide and hydrocyanic acid and subsequent heating yields an acid that passes on boiling with acetic anhydride into *i*-camphoric anhydride, from which the camphoric acid can be prepared in the usual manner Unfortunately, the yield of acid obtained is very poor.

$$
\begin{array}{ccc}
\begin{array}{l}
CH_2.COOH \quad COOH \\
\quad\quad\quad | \\
| \quad\quad C(CH_3)_2 \\
| \\
CH_2\text{------}CH.COOH
\end{array}
&\rightarrow&
\begin{array}{l}
CH_2.CO \\
| \\
| \quad\quad C(CH_3)_2 \\
| \\
CH_2.CH.COOH
\end{array}
\quad\rightarrow\quad
\begin{array}{l}
CH_2.C(CH_3)\text{---}O \\
| \quad\quad\quad\quad | \\
| \quad\quad C(CH_3)_2 \quad | \\
| \\
CH_2.CH\text{------}CO
\end{array}
\end{array}
$$

$$
\begin{array}{ccc}
\begin{array}{l}
CH_2.C(CH_3).COOH \\
| \\
| \quad\quad C(CH_3)_2 \\
| \\
CH_2.CH.COOH
\end{array}
&\leftarrow&
\begin{array}{l}
CH_2.C(CH_3).Br \\
| \\
| \quad\quad C(CH_3)_2 \\
| \\
CH_2.CH.COOH
\end{array}
\end{array}
$$
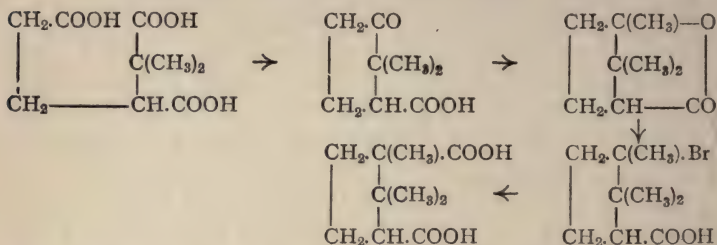
Homocamphoric acid $C_{11}H_{18}O_4$, the higher homologue of camphoric acid, was first obtained by Haller by the hydrolysis of cyancamphor,

$$
\begin{array}{ccccccc}
\begin{array}{l}
\text{---}CH_2 \\
| \\
C_8H_{14} \\
| \\
\text{---}CO
\end{array}
&\rightarrow&
\begin{array}{l}
\text{---}CHNa \\
| \\
C_8H_{14} \\
| \\
\text{---}CO
\end{array}
&\xrightarrow{CNCl}&
\begin{array}{l}
\text{---}CHCN \\
| \\
C_8H_{14} \\
| \\
\text{---}CO
\end{array}
&\rightarrow&
\begin{array}{l}
CH_2COOH \\
| \\
C_8H_{14} \\
| \\
COOH
\end{array}
\end{array}
$$
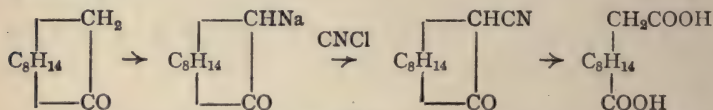
and later from camphoric anhydride by reduction to campholide, from which, by the addition of potassium cyanide, homocamphoric nitrile is obtained, the hydrolysis of the latter yielding homocamphoric acid.

$$
\begin{array}{ccccccc}
\begin{array}{l}
\text{---}CO \\
| \\
C_8H_{14} \quad O \\
| \\
\text{---}CO
\end{array}
&\rightarrow&
\begin{array}{l}
\text{---}CH_2 \\
| \\
C_8H_{14} \quad O \\
| \\
\text{---}CO
\end{array}
&\rightarrow&
\begin{array}{l}
CH_2CN \\
| \\
C_8H_{14} \\
| \\
COOH
\end{array}
&\rightarrow&
\begin{array}{l}
CH_2COOH \\
| \\
C_8H_{14} \\
| \\
COOH
\end{array}
\end{array}
$$
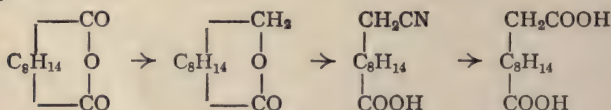
The distillation of its calcium or barium salt gives camphor (see Cap. II).

Isolaurolene, C_8H_{14}, is an unsaturated hydrocarbon of the cyclopentane series, which was obtained by Blanc on heating isolauronolic acid to $300°$ C., $C_8H_{13}.COOH = CO_2 + C_8H_{14}$. On oxidation with potassium permanganate it yields a dimethyl-hexanone carboxylic acid, and with potassium hypobromite $\alpha\alpha$-dimethyl glutaric acid. These results indicate that the hydrocarbon should possess the annexed formula.

$$
\begin{array}{ccc}
\begin{array}{l}
CH_2\text{------}CH_2 \\
| \\
| \quad\quad C(CH_3)_2 \\
| \\
COOH \quad COOH
\end{array}
&
\begin{array}{l}
CH_2\text{------}CH_2 \\
| \\
| \quad\quad C(CH_3)_2 \\
| \\
COOH \quad CO.CH_3
\end{array}
&
\begin{array}{l}
CH_2.\;CH_2 \\
| \\
| \quad\quad C(CH_3)_2 \\
| \\
CH : C.CH_3
\end{array}
\end{array}
$$

$\alpha\alpha$-dimethyl glutaric acid   Isolaurolene
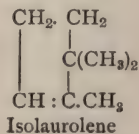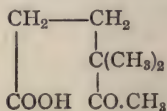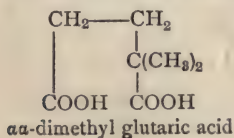
This has been confirmed recently (1906) by Blanc, who has synthesized the hydrocarbon, starting from γ-bromo-$\alpha\alpha$-dimethyl butyric ester, which on condensation with malonic ester yields $\alpha\alpha$-dimethyl adipic acid. This acid on treatment with acetic anhydride yields an anhydride which on distillation is converted into dimethylcyclopentanone, and from this by the action of the Grignard reagent the tertiary alcohol, trimethyl cyclopentanol, is obtained. The alcohol when distilled under diminished pressure readily loses a molecule of water and forms isolaurolene.

$$Br.CH_2.CH_2.C(CH_3)_2.COOH + CH_2(COOH)_2 = CH_2 - C(CH_3)_2.COOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2 - CH_2 - COOH$$

$$
\begin{array}{ccc}
\begin{array}{l} CH_2 - C(CH_3)_2 \\ \quad\ |\qquad\quad | \\ \quad\ CO \\ \quad\ |\qquad\quad | \\ CH_2 - CH_2 \end{array}
& +CO_2 \quad\leftarrow &
\begin{array}{l} CH_2 - C(CH_3)_2 - CO \\ \quad\ |\qquad\qquad\qquad | \\ \qquad\qquad\qquad O \\ \quad\ |\qquad\qquad\qquad | \\ CH_2 - CH_2 - CO \end{array}
\end{array}
$$

$$
\begin{array}{ccc}
\begin{array}{l} CH_2.C(CH_3)_2 \\ \quad\ |\qquad\quad | \\ \quad\ C(CH_3).OH \\ \quad\ |\qquad\quad | \\ CH_2.CH_2 \end{array}
& \rightarrow &
\begin{array}{l} CH_2.C(CH_3)_2 \\ \quad\ |\qquad\quad | \\ \quad\ C.CH_3 \\ \quad\ |\!|\qquad\quad | \\ CH_2.CH \end{array}
\end{array}
$$
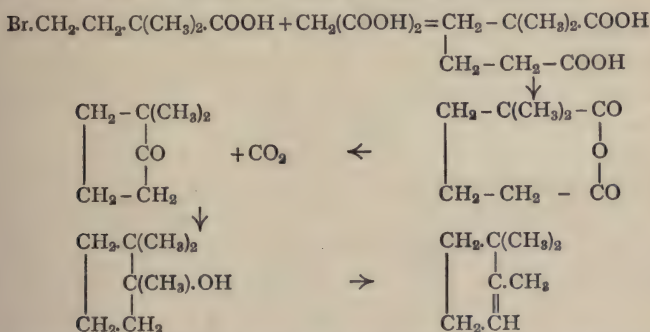
This series of reactions also leads to a synthesis of isolauronolic acid, since isolaurolene on treatment with acetyl chloride in the presence of aluminium chloride gives a ketone, which is then reduced to the corresponding secondary alcohol. Oxidation of this alcohol with nitric acid yields dihydroisolauronolic acid, and if this acid be then brominated and the elements of hydrobromic acid be eliminated from the resulting bromo-compound, isolauronolic acid, $C_9H_{14}O_2$, is obtained.

$$
\begin{array}{ccccc}
\begin{array}{l} CH.C(CH_3)_2 \\ \quad |\qquad\quad | \\ \quad C.CH_3 \\ \quad |\!|\qquad\quad | \\ CH_2.C.COCH_3 \end{array}
& \xrightarrow{H} &
\begin{array}{l} CH_2.C(CH_3)_2 \\ \quad |\qquad\quad | \\ \quad CH.CH_3 \\ \quad |\qquad\quad | \\ CH_2.CH.CH(OH).CH_3 \end{array}
& \xrightarrow{O} &
\begin{array}{l} CH_2.C(CH_3)_2 \\ \quad |\qquad\quad | \\ \quad CH.CH_3 \\ \quad |\qquad\quad | \\ CH_2.CH.COOH \end{array}
\end{array}
$$
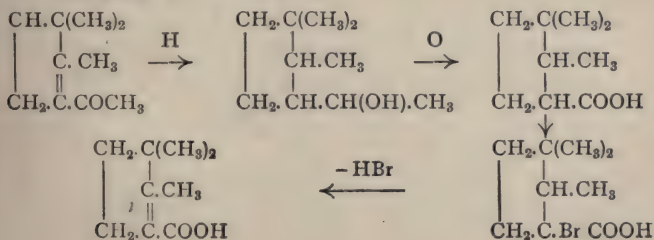
$$
\begin{array}{ccc}
\begin{array}{l} CH_2.C(CH_3)_2 \\ \quad |\qquad\quad | \\ \quad C.CH_3 \\ \quad |\!|\qquad\quad | \\ CH_2.C.COOH \end{array}
& \xleftarrow{-HBr} &
\begin{array}{l} CH_2.C(CH_3)_2 \\ \quad |\qquad\quad | \\ \quad CH.CH_3 \\ \quad |\qquad\quad | \\ CH_2.C.Br\ COOH \end{array}
\end{array}
$$

Campholene, C_9H_{16}, is also an unsaturated hydrocarbon of the cyclo-pentane series, and is obtained by the distillation of calcium α-campholenate or on heating β-campholenic acid with caustic soda. On oxidation with potassium permanganate it yields oxalic acid and dimethyl lævulinic acid, which led Tiemann to ascribe to it the following structure, and resulting decomposition on oxidation :—

$$
\begin{array}{c}
CH.CH.CH_3 \\
\| \quad | \\
C(CH_3)_2 \quad (I) \\
\| \quad | \\
CH.CH.CH_3
\end{array}
\xrightarrow{O}
\begin{array}{c}
COOH \\
| \\
| \\
COOH
\end{array}
+
\begin{array}{c}
CO.CH_3 \\
| \\
C(CH_3)_2 \\
| \\
CH_2.COOH.
\end{array}
$$
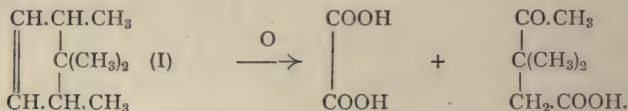
Bredt had at an earlier date given a different configuration (II), based on the preparation of the hydrocarbon from campholic acid and α-campholenic acid, whilst Bouveault and Blanc, on account of its preparation from β-campholenic acid, gave, in 1899, the formula represented in (III).

$$
\begin{array}{c}
CH_2.CH.CH_3 \\
| \quad | \\
C(CH_3)_2 \quad (II) \\
| \\
CH : C.CH_3
\end{array}
\qquad (III) \qquad
\begin{array}{c}
CH_2.CH_2 \\
| \quad | \\
C(CH_3)_2 \\
| \\
CH_3.C : C(CH_3)
\end{array}
$$
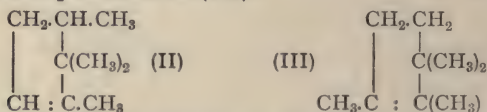
This last constitution appears to be the correct one, since campholene has been obtained synthetically in 1907 by Blanc in the following manner. The ethyl ester of γ-bromo-αα-dimethyl butyrate, on condensation with ethyl sodiomalonate, yields the ethyl ester of β-methylpentane-βεε-tricarboxylic acid. This ester is then methylated, the methylated product hydrolyzed, and the resulting acid heated, when ααδ-trimethyl adipic acid is formed. The anhydride of this acid on distillation yields 1.1.4-trimethyl cyclopentanone-5, from which, by means of the Grignard reagent, the corresponding tertiary alcohol is obtained. This alcohol on distillation loses water and gives campholene, thus :—

ROOC.C(CH₃)₂.CH₂.CH₂.Br + NaCH(COOR)₂
$\longrightarrow$ ROOC.C(CH₃)₂.CH₂.CH₂.CH(COOR)₂

HOOC.C(CH₃)₂.CH₂.CH₂.CH(CH₃).COOH

↑ Hydrolyse
─────────── ROOC.C(CH₃)₂.CH₂.CH₂.C(CH₃).(COOR)₂
and heat acid

Distil
↓ anhydride

$$\begin{array}{c} CH_2.CH_2 \\ | \quad\quad | \\ \quad C(CH_3)_2 \\ | \\ | \\ CH_3CH.CO \end{array} \quad \xrightarrow{CH_3MgI} \quad \begin{array}{c} CH_2CH_2 \\ | \quad\quad | \\ \quad C(CH_3)_2 \\ | \\ CH_3.CH.C(CH_3).OH \end{array} \quad \xrightarrow{distil} \quad \begin{array}{c} CH_2.CH_2 \\ | \quad\quad | \\ \quad C(CH_3)_2 \\ | \\ CH_3.C : C.CH_3 \end{array}$$
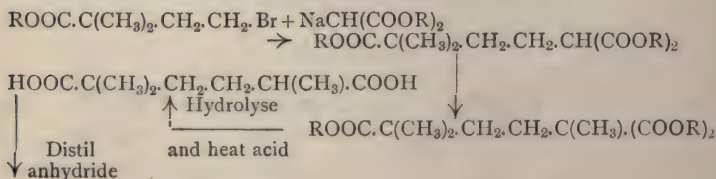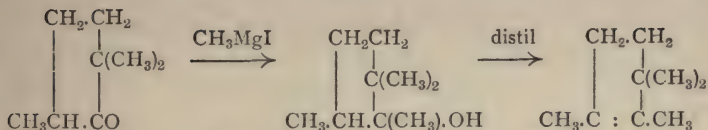
Camphorphorone, $C_9H_{14}O$, which is obtained on distilling calcium camphorate, is a keto-cyclopentane derivative—

$$C_8H_{14} : (CO_2)_2Ca = C_8H_{14} : CO + CaCO_3$$
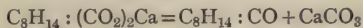
Its constitution follows, from its synthesis by Bouveault, by the action of sodium ethoxide on α-methylcyclopentanone and acetone, and consequently it must be a methylisobutylene cyclopentanone :—

$$\begin{array}{c} CH_2.CH_2 \\ | \quad\quad | \\ \quad CO \\ | \\ CH_2.CH(CH_3) \end{array} \quad + \quad (CH_3)_2CO = H_2O \quad + \quad \begin{array}{c} CH_2.C:C(CH_3)_2 \\ | \quad\quad | \\ \quad CO \\ | \\ CH_2.CH.CH_3 \end{array}$$
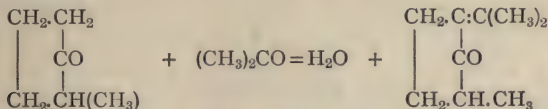
The reverse process takes place when camphorphorone is heated with solid caustic potash. It combines directly with hydroxylamine to form a hydroxylamino derivative, the group $> C = C(CH_3)_2$ being transformed into $> CH - C(NHOH)(CH_3)_2$, such a reaction being shown by Harries and Roeder to be characteristic of this type of unsaturated ketone.

The fulvenes are a series of unsaturated hydrocarbons of a deep yellow or red colour, which were first obtained by Marckwald on condensing aldehydes with indene, and later by Thiele by the condensation of cyclopentadiëne with aldehydes and ketones in the presence of sodium ethoxide. They may thus be considered as derivatives of the as yet unknown hydrocarbon fulvene, in which it may be noted that

$$\begin{array}{c} HC:CH \\ | \quad\quad | \quad ^* \\ \quad C:CH_2 \\ | \\ HC:CH \end{array}$$
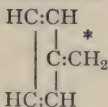
one has a system of linkages comparable with that in benzoquinone, that is to say, a grouping of a chromophoric character. The fulvenes derived from the ketones and cyclopentadiene are more stable than those derived from the aldehydes and the hydrocarbon. Thiele has shown that those fulvenes which

possess a phenyl or carboxyl group attached to the carbon atom
C^* are readily reduced by the aluminium mercury couple and
yield colourless derivatives, benzylidene indene, for example,
yielding benzyl indene.

$$
\begin{array}{ccc}
\mathrm{C_6H_4 - C:CHC_6H_5} & & \mathrm{C_6H_4 - C.CH_2C_6H_5} \\
| \quad\quad | & \rightarrow & | \quad\quad \| \\
\mathrm{CH = CH} & & \mathrm{CH_2 - CH}
\end{array}
$$
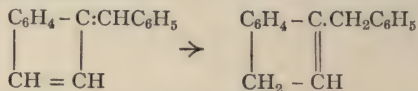
This reduction seems also to depend on the presence of the
cyclopentadiene ring, since bis-diphenylene ethylene is reducible,
whilst tetraphenyl ethylene is not.

Cyclohexanes.—Many of the members of this group will be
considered under Terpenes (Cap. II), more particularly those
derived from methyl-1-isopropyl-4-cyclohexane or hexahydro-
cymene, $C_{10}H_{20}$, which may be looked upon as the parent
substance of many of the monocyclic terpenes. This hydrocarbon
may be obtained by the reduction of menthyl chloride with sodium
and alcohol, or by the reduction of limonene, cymene, etc., with
hydrogen in the presence of reduced nickel by the Sabatier and
Senderens method.

The ketones are perhaps the most important derivatives of this
series, since some of them are closely related to the monocyclic
terpenes. Cyclohexanone, $C_6H_{10}O$, the first member of the series,
was obtained by Wislicenus by the distillation of calcium pime-
late. It has also been obtained by the electrolytic reduction of
phenol, and recently the process has been reversed in such a way
that the intermediate products could be isolated, showing the
gradual transition from the saturated ring system to the ordinary
aromatic ring system. In this change the ketone is brominated,
and hydrobromic acid is eliminated from the resulting bromo-
compound. The unsaturated hexenone so formed, readily takes
up two atoms of bromine, and if now hydrobromic acid be
removed from the dibromide, phenol is obtained.

$$
\begin{array}{ccccc}
\mathrm{CH_2.CH_2.CO} & & \mathrm{CH_2.CH_2.CO} & & \mathrm{CH_2.CH_2.CO} \\
| \quad\quad | & \rightarrow & | \quad\quad | & \rightarrow & | \quad\quad | \\
\mathrm{CH_2.CH_2.CH_2} & & \mathrm{CH_2.CH_2.CHBr} & & \mathrm{CH_2CH:CH} \\
& & & & \downarrow \\
& \mathrm{CH.CH:C(OH)} & & \mathrm{CH_2.CH_2.CO} \\
& \| \quad\quad | & \leftarrow & | \quad\quad | \\
& \mathrm{CH.CH:CH} & & \mathrm{CH_2.CHBr.CHBr}
\end{array}
$$
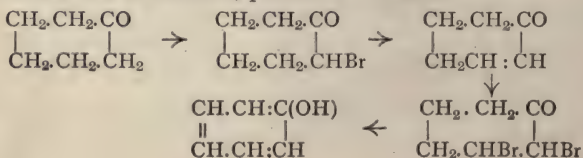
Cyclohexanone condenses readily with monochloroacetic ester in the presence of sodium ethoxide to form a glycide ester which on hydrolysis yields the free acid. This acid on distillation in vacuo loses carbon dioxide and is converted into hexahydro-benzaldehyde.

$$CH_2.CH_2.CO \atop CH_2.CH_2.CH_2 \qquad Cl.CH_2COOR \longrightarrow \qquad {\overset{\displaystyle O}{\overset{\displaystyle \wedge}{CH_2.CH_2.C-CH.COOR}} \atop CH_2.CH_2.CH_2}$$

$$CH_2.CH_2.CH.CHO \atop CH_2.CH_2.CH_2 \quad + \quad CO_2. \quad \overset{\text{hydrolysis}}{\underset{\text{and distillation}}{\longleftarrow}}$$
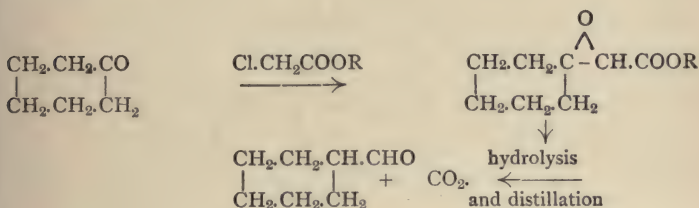
Of the three possible methylcyclohexanones, the methyl-1-cyclo-hexanone-3 is the most important, since it arises from the hydrolysis of pulegone.

$$CH_3.CH.CH_2.CO \atop CH_2.CH_2.C:C(CH_3)_2 \quad + \quad H_2O \quad = \quad {CH_3.CH.CH_2.CO \atop CH_2.CH_2.CH_2} \quad + \quad (CH_3)_2CO.$$
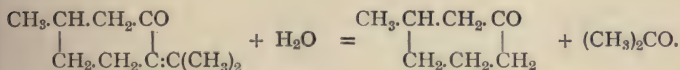
The product obtained in this way represents the d-form, whilst the racemic variety is obtained by the distillation of the calcium salt of β-methyl pimelic acid. On oxidation with nitric acid, both varieties yield a mixture of α- and β-adipic acids. Successive treatment with sodamide and the alkyl iodides converts it into homologues to menthone. Wallach has shown that it may be converted into the isomeric methyl-1-cyclohexanone-2, by the following series of reactions. The cyclohexanol formed by reduction, loses water when heated with phosphorus pentoxide, and is converted into methyl cyclohexene, the nitrosate of which, when heated with sodium methoxide, yields two isomeric oximes, and from these on hydrolysis one and the same methylhexenone is formed. This hexenone is then reduced by sodium and alcohol to the cyclohexanol from which the ketone is obtained by oxidation,

$$\begin{array}{ccc}
CH_2.CH_2.CH.CH_3 & CH_2.CH_2 \ . \ CH.CH_3 & CH_2.CH_2.C.CH_3 \\
| \qquad \ | & | \qquad \qquad | & | \qquad \ \ || \\
CH_2.\ CO\ .\ CH_2 \rightarrow & CH_2.CHOH.CH_2 \ \text{-}\rightarrow & CH_2.CH_2.CH
\end{array}$$

$$\downarrow$$

$$\begin{array}{ccc}
CH_2.CH:C.CH_3 & CH_2.CH:C.CH_3 & CH_2.CH_2.C{<}^{CH_3}_{NO_3} \\
| \qquad \quad | & | \qquad \quad | & | \qquad \qquad | \\
CH_2.CH_2.\overset{\cdot}{C}O \leftarrow & CH_2.CH_2.C:NOH \leftarrow & CH_2.CH_2.C:NOH
\end{array}$$

$$\downarrow$$

$$\begin{array}{cc}
CH_2.CH_2.CH.CH_3 & CH_2.CH_2.CH.CH_3 \\
| \qquad \qquad | & | \qquad \qquad | \\
CH_2.CH_2.CHOH \rightarrow & CH_2.CH_2.CO
\end{array}$$
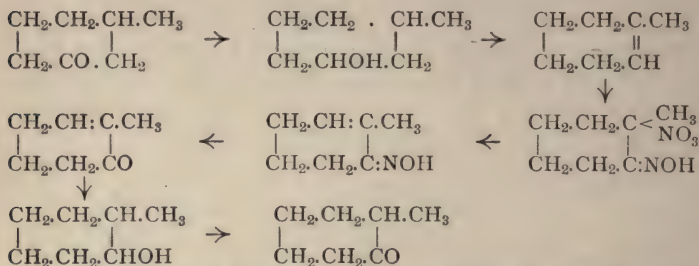
Methyl-1-cyclohexanone-4 acquires a theoretical interest since Perkin has shown that with the Grignard reagent it can be converted into tertiary menthol. The starting-point in this transformation is α-bromohexahydroparatoluic acid, which is decomposed by sodium carbonate into Δ.1-tetrahydroparatoluic acid and α-hydroxyhexahydroparatoluic acid, the latter being converted into the cyclohexanone by the action of dilute sulphuric acid.

$$\begin{array}{ccc}
CO_3.CH.CH_2.CH_2 & CH_3.CH.CH_2.CH_2 & CH_3.CH.CH_2.\ CH_2 \\
| \qquad \qquad \ | & | \qquad \qquad | & | \qquad \qquad | \\
CH_2.CH_2.C(Br).COOH \rightarrow & CH_2.CH_2.C(OH).COOH \rightarrow & CH_2.CH_2.CO
\end{array}$$
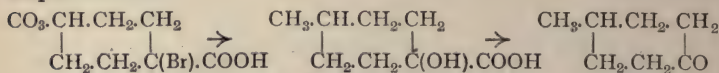
On condensation with magnesium isopropyl iodide and subsequent hydrolysis it is converted into tertiary menthol. Wallach has also shown that on treatment with isobutyric acid and zinc it is converted into an oxy-ester which loses water easily, and if the resulting unsaturated ester be hydrolyzed and the free acid heated, carbon dioxide is eliminated and i-Δ.4(8)-menthene is obtained.

$$\begin{array}{cc}
CH_2.CH_2.CO & CH_2.CH_2.C(OH).C(CH_3)_2.COOR \\
| \qquad \quad | & | \qquad \qquad | \\
CH_3.CH.CH_2.CH_2 \rightarrow & CH_3.CH.CH_2.\ CH_2
\end{array}$$

$$\downarrow$$

$$\begin{array}{cc}
CH_2.CH_2.C:C(CH_3)_2 & CH_2.CH:C.C(CH_3)_2.COOR \\
| \qquad \qquad | & | \qquad \qquad | \\
CH_3.CH.\ CH_2.CH_2 \leftarrow & CH_3.CH.CH_2.CH_2
\end{array}$$
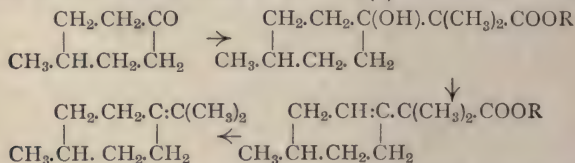
It may be mentioned in passing that two types of cyclohexenones exist, namely the αβ and βγ hexenones, the isomerism depending on the position of the double linkage, thus—

$$\begin{array}{cc}
CH_2.CH_2.CH & CH_2.CH:CH \\
| \qquad \quad || & | \qquad \quad || \\
CH_2.CO\ .\ CH & CH_2.CO.CH_2 \\
\alpha\beta & \beta\gamma
\end{array}$$

These two groups show characteristic differences in their behaviour to reagents, the $\alpha\beta$ compounds, for example, on reduction with zinc and alcoholic potash, yielding saturated ketones and also bimolecular compounds, in which two molecules are linked together through the β-carbon atom, whilst the $\beta\gamma$ compounds are unaffected. Again, the $\beta\gamma$ series react in the normal manner with hydroxylamine to form oximes, whilst the $\alpha\beta$ series form oxamino-oximes, the group $-CH=CH-CO-$ becoming $-HC(NHOH)-CH_2-C(:NOH)-$. These oxamino compounds may also be of two different types, depending on whether the group $-NHOH$ is united to a secondary or a tertiary carbon atom, and for this reason show a characteristic behaviour on oxidation. Those of the former type on oxidation yield colourless dioximes, whilst the latter yield nitroso compounds which give the usual characteristic blue solutions; thus—

$$\text{HOHN.CH.CHR.C:NOH} \quad \rightarrow \quad \text{HON:C.CHR.C:NOH}$$

$$\text{HOHN.CR.CH}_2\text{.C:NOH} \quad \rightarrow \quad \text{ON.CR.CH}_2\text{.C:NOH}$$
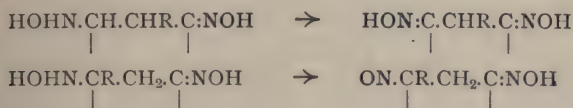
Two naturally occurring compounds of the cyclohexane series are sedanonic acid, $C_{12}H_{18}O_3$, and sedanolic acid, $C_{12}H_{20}O_3$, which were found by Ciamician and Silber in the higher boiling fractions of celery oil. The constitution of these substances has been worked out in the following manner. On reduction with sodium amalgam, both yield the same product, an alcohol acid, $C_{12}H_{22}O_3$ (orthohydroxyamyl hexahydrobenzoic acid), consequently both contain the same carbon nucleus. Again, sedanonic acid behaves as an unsaturated ketonic acid, and its oxime readily undergoes the Beckmann transformation on warming with concentrated sulphuric acid, yielding n-butyl tetrahydrophthalamic acid, which is easily hydrolyzed to n-butylamine and $\Delta.2$-tetrahydrophthalic acid. And since potassium permanganate oxidizes sedanonic acid to oxalic, glutaric, and n-valeric acids, it follows that the ethylene linkage must be next to the carboxyl group. Thus one has

$$\underset{\substack{\text{Oxime of sedanonic acid}}}{\overset{\displaystyle C(:NOH).C_4H_9}{\underset{\displaystyle COOH}{\overset{\displaystyle |}{\underset{\displaystyle |}{C_6H_8}}}}} \rightarrow \underset{\substack{}}{\overset{\displaystyle CONH.C_4H_9}{\underset{\displaystyle COOH}{\overset{\displaystyle |}{\underset{\displaystyle |}{C_6H_8}}}}} \overset{H_2O}{\rightarrow} \overset{\displaystyle CH_2.CH:C.COOH}{\underset{\displaystyle CH_2.CH_2.CH.COOH}{\overset{\displaystyle |}{\underset{\displaystyle +C_4H_9NH_2}{|}}}}$$
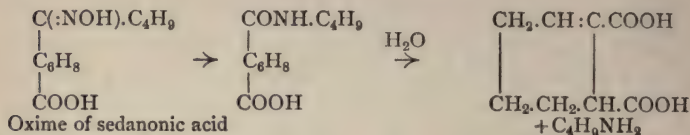
whence sedanonic acid must be orthovaleryl-Δ-1-tetrahydrobenzoic acid.

$$\overset{\displaystyle CH_2.CH:C.COOH}{\underset{\displaystyle CH_2.CH_2.CH.CO.C_4H_9}{\overset{\displaystyle |}{\underset{\displaystyle |}{}}}}$$
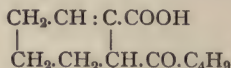
Again, sedanolic acid is readily oxidized by alkaline potassium permanganate to ortho-hydroxyamyl benzoic acid, which readily passes into its lactone butyl phthalide; and since it possesses the same carbon nucleus as sedanonic acid, it is to be considered as an ortho-hydroxyamyl-Δ.5-tetrahydrobenzoic acid, the latter series of changes taking place thus :—

$$\underset{\substack{\text{Sedanolic acid}}}{\overset{\displaystyle CH_2.CH_2.CH.COOH}{\underset{\displaystyle CH_2.CH:C.CHOH.C_4H_9}{\overset{\displaystyle |}{\underset{\displaystyle |}{}}}}} \rightarrow \underset{\substack{\text{Hydroxy-amyl benzoic acid}}}{\overset{\displaystyle CH.CH:C.COOH}{\underset{\displaystyle CH.CH:C.CHOH.C_4H_9}{\overset{\displaystyle \|}{\underset{\displaystyle \|}{}}}}} \rightarrow \underset{\substack{\text{Butyl phthalide}}}{\overset{\displaystyle CH.CH:C.CO}{\underset{\displaystyle CH.CH:C.CH.C_4H_9}{\overset{\displaystyle \|}{\underset{\displaystyle \|}{}}}}O}$$
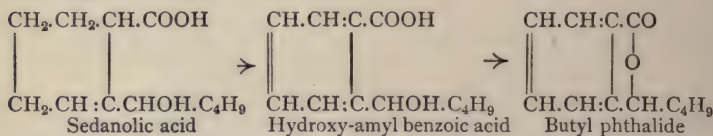
Sedanolic acid readily splits out a molecule of water between the – COOH and – OH groups, and passes into its lactone sedanolid, $C_{12}H_{18}O_2$, a colourless thick oil which is the odoriferous constituent of celery oil.

Diosphenol, $C_{10}H_{16}O_2$, which is found in the essential oil of Bucco leaves, is an unsaturated ketone alcohol of the cyclohexane series. It was formerly thought to be a hydroxyaldehyde, but its synthesis from hydroxymethylene menthone has shown that it must be regarded as a hydroxy-ketone. Oxymethylene menthone is readily oxidized by ozone to the corresponding methyl-1-isopropyl-4-cyclohexane-dione-2.3, which, on treatment with acids or alkalies, rearranges itself to diosphenol, thus :—

$$\overset{\displaystyle CH_2.CH_2.CH.CH_3}{\underset{\displaystyle C_3H_7.CH.CO.CH:CHOH}{\overset{\displaystyle |}{\underset{\displaystyle |}{}}}} \rightarrow \overset{\displaystyle CH_2.CH_2.CH.CH_3}{\underset{\displaystyle C_3H_7.CH.CO.CO}{\overset{\displaystyle |}{\underset{\displaystyle |}{}}}} \rightarrow \overset{\displaystyle CH_2.CH_2.C.CH_3}{\underset{\displaystyle C_3H_7.CH.CO.C.OH}{\overset{\displaystyle |}{\underset{\displaystyle \|}{}}}}$$
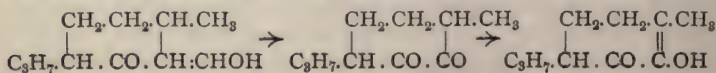
On reduction it gives paramenthane-diol-2.3, whilst ozone oxidizes it to α-isopropyl-γ-acetyl butyric acid,

$$CH_3CO.CH_2.CH_2.CH(C_3H_7)COOH.$$
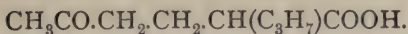
When heated in a sealed tube with hydrochloric acid it gives an almost quantitative yield of thymol.

Cycloheptanes—In this group the most important derivatives are those which have been obtained by the breaking down of the tropine molecule, a series of unsaturated hydrocarbons and their derivatives being produced according to the conditions of experiment. Many of these compounds have been synthesized in recent years by Willstätter.

Cycloheptane C_7H_{12} results when suberone oxime is reduced to cycloheptane amine, which is then subjected to the destructive methylation process of Hofmann (see *Alkaloids*), or as an alternative cycloheptane carboxylic acid, which is obtained in the breaking down of the hydroecgonidine molecule (see *Alkaloids*), may be converted into its amide, which on treatment with bromine and alkali yields cycloheptane amine.

$$\begin{array}{ccc}
CH_2.CH_2.CO & & CH_2.CH_2.C{:}NOH \\
| \qquad | & \rightarrow & | \qquad | \\
| \quad CH_2 & & | \quad CH_2 \\
| \qquad | & & | \qquad | \\
CH_2.CH_2.CH_2 & & CH_2.CH_2.CH_2
\end{array}$$

$$\begin{array}{ccccc}
CH_2.CH_2.CH.NH_2 & \leftarrow & CH_2.CH_2.CH.CONH_2 & & CH_2.CH_2.CH.COOH \\
| \qquad | & & | \qquad | & & | \qquad | \\
| \quad CH_2 & \leftarrow & | \quad CH_2 & \leftarrow & | \quad CH_2 \\
| \qquad | & & | \qquad | & & | \qquad | \\
CH_2.CH_2.CH_2 & & CH_2.CH_2.CH_2 & & CH_2.CH_2.CH_2
\end{array}$$

$$\downarrow \begin{array}{l} CH_3I \\ \text{then } Ag_2O(H_2O) \end{array}$$

$$\begin{array}{ccc}
CH_2.CH_2.CH.N(CH_3)_3.OH & & CH_2.CH_2.CH \\
| \qquad | & \xrightarrow{\text{distil}} & | \qquad \| \\
| \quad CH_2 & & | \quad CH \\
| \qquad | & & | \qquad | \\
CH_2.CH_2.CH_2 & & CH_2.CH_2.CH_2
\end{array} + H_2O + N(CH_3)_3$$
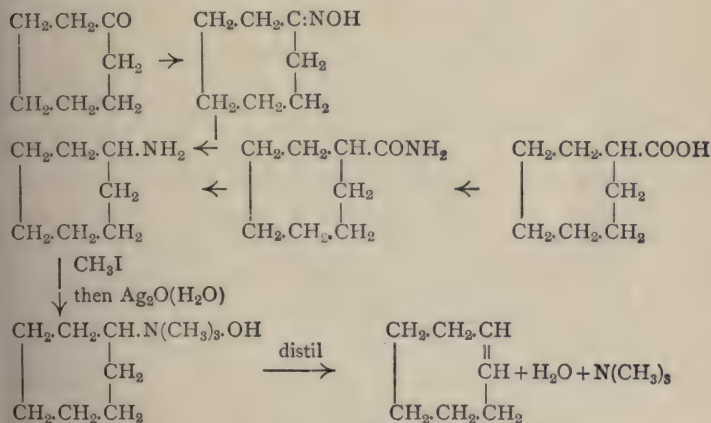
This hydrocarbon yields a dibromide which condenses with dimethylamine to form dimethylaminocycloheptene, and the amino-compound by destructive methylation, and distillation of the corresponding ammonium hydroxide is converted into a cycloheptadiene-1-3, C_7H_{10}. This hydrocarbon in its turn, by the addition of bromine and subsequent heating of the dibromide

3

with quinoline, was converted by Willstätter into cycloheptatriene C_7H_8, which had first been obtained by Ladenburg (and called by him tropilidene) as a decomposition product of tropine.

$$
\begin{array}{ccc}
\underset{|}{\text{CH}_2\text{.CH}_2\text{.CHBr}} & & \underset{|}{\text{CH}_2\text{.CH}_2\text{.CHN(CH}_3)_2} \\
\overset{|}{}\text{CHBr} & \xrightarrow{\ \text{NH(CH}_3)_2\ } & \overset{|}{}\text{CH} \\
\underset{}{} & & \overset{\|}{} \\
\text{CH}_2\text{.CH}_2\text{.CH}_2 & & \text{CH}_2\text{.CH}_2\text{.CH}
\end{array}
$$

exhaustive ← methylation
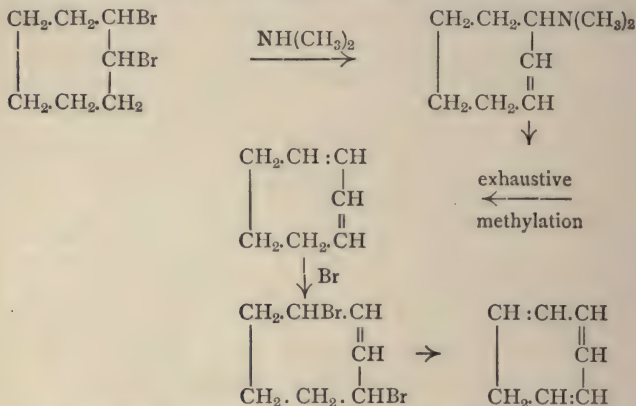
Further details of the related compounds will be given in the discussion of the constitution of tropine (p. 146).

The isophenylacetic acids may be mentioned here, since, according to the investigations of Buchner, they are to be regarded as cycloheptatriene carboxylic acids, although at one time regarded as being methylene dihydrobenzoic acids. All four possible isomers are known and have been assigned the following constitutions :—
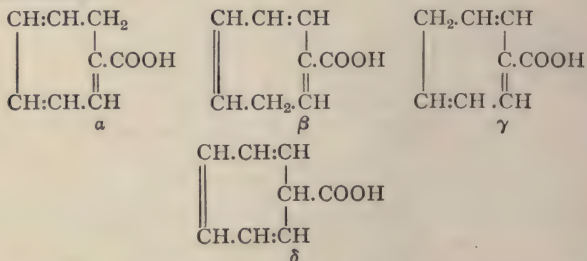
By the condensation of diazoacetic ester with benzene at about 130° C., a ψ-phenylacetic ester is obtained which, on long standing with concentrated ammonia, is converted into ψ-phenylacetamide

and from this latter compound by hydrolysis with caustic soda, the free α-isophenylacetic acid is obtained. The reactions may be expressed thus :—

$$CHN_2.COOR + \begin{array}{c} CH.CH:CH \\ \| \quad | \\ CH.CH:CH \end{array} \rightarrow ROOC.CH \begin{array}{c} \text{—CH.CH:CH} \\ | \\ \text{—CH.CH:CH} \end{array}$$

$$\downarrow$$

$$\begin{array}{c} CH. \quad CH:CH \\ \| \quad | \\ HOOC.C \quad | \\ CH_2.CH:CH \end{array} \leftarrow H_2N.CO.CH \begin{array}{c} \text{—CH.CH:CH} \\ | \\ \text{—CH.CH:CH} \end{array}$$
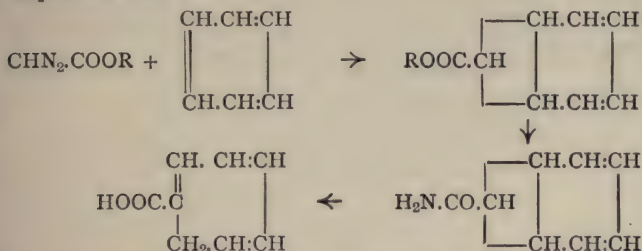
whilst if the ψ-phenylacetic ester be heated in an evacuated tube to 150° C., the ester of the isomeric β-acid is obtained, from which the free acid results on hydrolysis. This β-acid is also formed when the methiodide of ecgonine ethyl ester is hydrolyzed with dilute caustic alkali. The α-acid contains three double linkages, since it combines with six atoms of hydrogen and yields as ultimate reduction product the saturated hexahydroisophenylacetic acid $C_7H_{13}COOH$, and since this acid contains two less hydrogen atoms than the corresponding octane acid $C_7H_{15}COOH$ it must in all probability possess a cyclic structure. Again, the amide of this hexahydroisophenylacetic acid is identical with the amide of suberone carboxylic acid which results when suberone is condensed with hydrocyanic acid and the resulting nitrile is hydrolyzed to the hydroxy-acid. This acid on treatment with phosphorus pentachloride yields a chlorinated acid, from which suberone carboxylic acid is obtained by reduction.

$$\begin{array}{c} CH_2.CH_2.CH_2 \\ | \quad CO \\ CH_2.CH_2.CH_2 \end{array} \rightarrow \begin{array}{c} CH_2.CH_2.CH_2 \\ | \quad C(OH).CN \\ CH_2.CH_2.CH_2 \end{array} \rightarrow \begin{array}{c} CH_2.CH_2.CH_2 \\ | \quad C(OH).COOH \\ CH_2.CH_2.CH_2 \end{array}$$

$$\downarrow$$

$$\begin{array}{c} CH_2.CH_2.CH_2 \\ | \quad CH.COOH \\ CH_2.CH_2.CH_2 \end{array} \leftarrow \begin{array}{c} CH_2.CH_2.CH_2 \\ | \quad C(Cl).COOH \\ CH_2.CH_2.CH_2 \end{array}$$
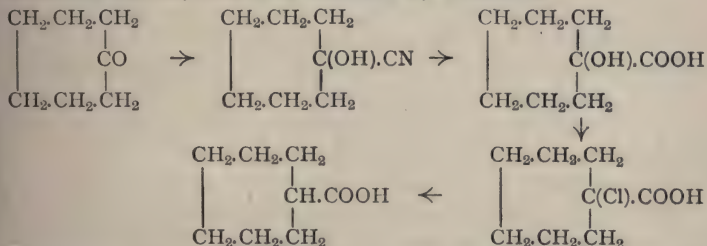
Consequently, the α-isophenylacetic acid contains a seven carbon

ring. The position of the double linkages is shown by the fact that the dihydrobromide of the α-acid on reduction, first by zinc dust and alcoholic hydrochloric acid, and finally by zinc dust and glacial acetic acid, gives Δ.1-cycloheptene carboxylic acid, which has been obtained synthetically.

$$
\begin{array}{ccc}
\overset{\displaystyle CH:CH.CH}{\underset{\displaystyle CH:CH.CH}{\big|\quad\overset{\displaystyle C.COOH}{\big\|}}} & \rightarrow & \overset{\displaystyle CH_2.CHBr.CH_2}{\underset{\displaystyle CH_2.CHBr.CH}{\big|\quad\overset{\displaystyle C.COOH}{\big\|}}} \\
 & & \downarrow \\
\overset{\displaystyle CH_2.CH_2.CH_2}{\underset{\displaystyle CH_2.CH_2.CH}{\big|\quad\overset{\displaystyle C.COOH}{\big\|}}} & \leftarrow & \overset{\displaystyle CH_2.CH_2.CH_2}{\underset{\displaystyle CH_2.CHBr.CH}{\big|\quad\overset{\displaystyle C.COOH}{\big\|}}}
\end{array}
$$
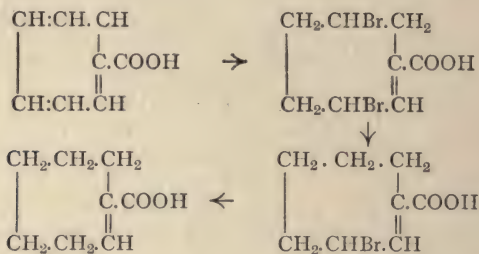
The β-acid yields a dihydrobromide identical with that obtained from the α-acid, and so contains the same carbon nucleus. On reduction it yields Δ.2-cycloheptene carboxylic acid.

γ-Isophenylacetic acid is formed when the β-acid is heated for many hours with alcoholic potash, whilst the δ-acid is obtained by the action of silver oxide and water on the methiodide of anhydro-ecgonine ester, the intermediate product being decomposed by boiling with caustic alkali. On reduction it yields Δ.2-cycloheptene carboxylic acid.

Cyclo-octanes—Very few members of this group have as yet been isolated. ψ-Pelletierine, one of the alkaloids of the pomegranate, on destructive methylation yields a cyclo-octadiene C_8H_{12} as an unstable compound which rapidly polymerizes. A β-cyclo-octadiene of a much more stable character has been described, and is prepared from methyl granatinine methiodide (see *Alkaloids*). When reduced by the Sabatier and Senderens method it yields cyclo-octane C_8H_{16}, a liquid with a strong camphor odour, and which on oxidation yields suberic acid.

Doebner has also prepared compounds, which are probably to be considered as cyclo-octadienes, by the distillation of β-vinyl-acrylic acid and cinnamenylacrylic acid with anhydrous baryta.

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CHAPTER II

THE TERPENES AND CAMPHORS

THE terpene group of compounds consists of a series of cyclic hydrocarbons of the general formula $(C_5H_8)_n$ and the oxygenated substances which are chiefly of an alcoholic, aldehydic or ketonic nature, derived from them. The parent hydrocarbons are capable of division into distinct groups, and may be classified as (a) *Hemiterpenes*, which correspond to the molecular formula C_5H_8 ; (b) *Terpenes* proper, corresponding to $C_{10}H_{16}$; (c) *Sesquiterpenes* corresponding to $C_{15}H_{24}$, and (d) *Polyterpenes* corresponding to $(C_5H_8)_n$. In addition to the above groups of compounds, another series has been discovered in recent years, namely, that of the open chain olefine hydrocarbons $(C_5H_8)_2$ and the aldehydes, ketones, and alcohols derived from them.

In the following pages, the olefine terpene series will be considered first. The alcohols and aldehydes of this series are found to exist in many essential oils, more especially in oil of lemons, oil of oranges, and the oils of geranium, neroli, petitgrain, linaloe, coriander ; lemon grass oil, and in Turkish and German rose oil. One of the most important derivatives of this series is *citral* (geranial) $C_{10}H_{16}O$, an aldehyde obtained largely from essence of lemon grass, from which it may be isolated by means of its bisulphite compound by working at a low temperature. The bisulphite compound is decomposed by alkaline carbonates in the usual manner, and the small quantity of methyl heptenone, which is generally present, is then separated by fractional distillation. It may be prepared artificially by the usual methods, namely, by oxidation of the corresponding alcohol (geraniol), or by distilling a mixture of calcium formate and calcium geraniate. Since geranic acid has been itself synthesized

we are in possession of a complete synthesis of citral. The key to the synthesis of the aldehyde was first found by a study of its decomposition products, particularly those of its oxidation with potassium permanganate, whereby it yields lævulinic acid, acetone, and carbon dioxide; and of its hydrolysis with potassium carbonate when it yields acetaldehyde and methyl-heptenone.

$$(CH_3)C:CH.CH_2.CH_2.CO.CH_3 + CH_3CHO$$
$$\uparrow$$
$$C_8H_{16}O$$
$$\downarrow$$
$$CH_3.CO.CH_3 + CH_3.CO.CH_2.CH_2.COOH + CO_2.$$
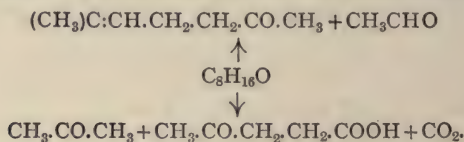
These results show the unsaturated nature of the aldehyde (which is also determined by the formation of addition products) and enable the position of the ethylene linkages to be fixed as shown in the annexed formula

$$\overset{(a)}{(CH_3)_2C}:CH.CH_2.CH_2.\overset{(b)}{C}(CH_3):CH.CHO$$
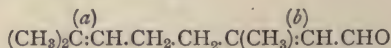
oxidation taking place at a and b, hydrolysis at b alone.

The synthesis of geranic acid took for its starting point methyl-heptenone, which was previously prepared by Barbier and Bouveault by the condensation of *gem*-dimethyltrimethylene bromide with sodium acetylacetone and decomposition of the resulting ketone with concentrated sodium hydroxide solution

$$(CH_3)_2.CBr.CH_2.CH_2.Br$$
$$\Big| \quad CH_3COCH_2COCH_3$$
$$\downarrow$$
$$(CH_3)_2.C:CH.CH_2.CH(COCH_3)_2 \; \rightarrow \; (CH_3)_2C:CH.CH_2.CH_2.CO.CH_3$$
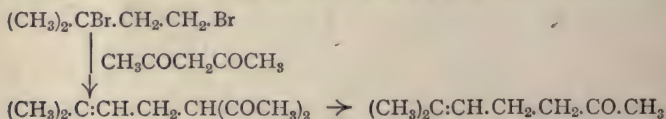
and also by Ipatiew from the same bromo-compound and sodium aceto-acetate the *gem*-dimethylallylacetoacetic ester being hydrolyzed by caustic baryta.

$$CH_3)_2.CBr.CH_2.CH_2.Br \quad \rightarrow \quad (CH_3)_2C:CH.CH_2.Br + HBr$$
$$\downarrow$$
$$(CH_3)_2C:CH.CH_2.CH_2.CO.CH_3 \; \leftarrow \; (CH_3)_2.C:CH.CH_2.CH \!<^{COCH_3}_{COOR}$$
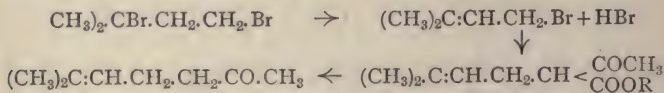
The methyl heptenone thus produced condenses with iodo-acetic acid in the presence of metallic zinc to form an addition compound which hydrolyzes in the presence of dilute acids to an

unsaturated hydroxy-acid, and this latter on heating loses a molecule of water and passes into geranic acid.

$$(CH_3)_2.C:CH.CH_2.CH_2.CO.CH_3 + ICH_2.COOH$$
$$\downarrow Zn$$
$$CH_3$$
$$|$$
$$(CH_3)_2C:CH.CH_2.CH_2.C.CH_2.COOH$$
$$|$$
$$OZnI$$
$$\downarrow$$
$$(CH_3)_2C:CH.CH_2.CH_2.C(OH)(CH_3).CH_2.COOH$$
$$\downarrow$$
$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.COOH + H_2O$$
$$\text{geranic acid}$$
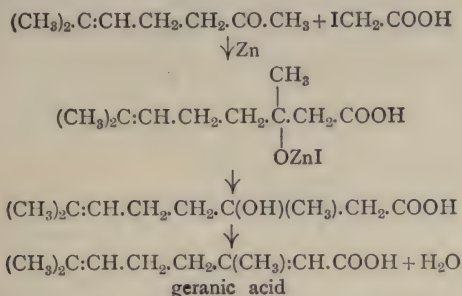
Citral is converted into cymene by the action of acid condensation agents, the ring closing between the third and eighth carbon atoms of the chain.

$$CH_3CH:CH.CHO \qquad\qquad CH_3.C:CH.CH$$
$$| \qquad\qquad\qquad \rightarrow H_2O + \qquad | \quad ||$$
$$CH_2.CH_2.CH:C(CH_3)_2 \qquad\qquad HC:CH.C.CH(CH_3)_2$$
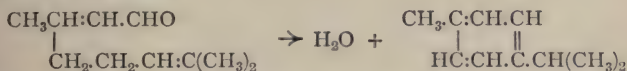
It has been shown that crude citral is a mixture of two isomers, citral-a and citral-b, since two different semicarbazones may be obtained from the mixture and two different citrylidene-cyanacetic acids. The two are stereoisomers, since Harries in 1907 showed their structural identity by converting them into ozonides (by passing ozone into their solution in carbon tetrachloride) and found that the decomposition of these ozonides in each case gave rise to the same products, namely, acetone, glyoxal and lævulinic aldehyde, from which it follows that the two are of a similar structure.

$$(CH_3)_2.C\!\!-\!\!-\!\!CH.CH_2.CH_2.C(CH_3\,CH.CHO$$
$$O_3 \qquad\qquad\qquad O_3$$
$$\downarrow$$
$$CH_3COCH_3 + OHC.CHO + OHC.CH_2.CH_2.CO.CH_3$$
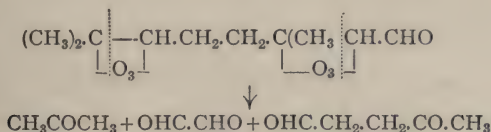
The two isomers exist in very different proportions in the crude oils, the a variety occurring to about the extent of $73°/_0$ and the b variety to about $8°/_0$ in lemon grass oil.

It was shown above that citral may be readily converted into cymene by acid reagents, but it is found that if the reactivity of the carbonyl group is reduced by replacement of the carbonyl oxygen, then the condensation undergoes another course, the ring closing between the carbon atoms in positions 2 and 7, yielding cyclic isomers.

$$\underset{\underset{\displaystyle CH_3}{|}}{\overset{1}{CH_3}.\overset{2}{C}:\overset{3}{CH}.\overset{4}{CH_2}.\overset{5}{CH_2}.\underset{\underset{\displaystyle CH_3}{|}}{\overset{6}{C}}:\overset{7}{CH}.R} \quad \rightarrow \quad (CH_3)_2.\underset{\underset{\displaystyle R.C=\!=\!C.CH_3}{|}}{\overset{\overset{\displaystyle CH_2-CH_2}{|\qquad|}}{C}}\ \overset{\displaystyle}{CH_2}$$

These cyclic isomers may exist in two isomeric forms, the α-series and the β-series, the isomerism being due to the position of the double linkage in the molecule, thus taking geranic acid as an example, two cyclo-geranic acids may be prepared.

$$\underset{\underset{\displaystyle CH_3}{|}}{CH_3.C}:CH.CH_2.CH_2.\underset{\underset{\displaystyle CH_3}{|}}{C}:CH.COOH$$

$$\downarrow$$

$$(CH_3)_2.C.OH \qquad\qquad CH_2.COOH$$
$$|\qquad\qquad\qquad\qquad\qquad\;|$$
$$CH_2$$
$$|$$
$$CH_2\!\!-\!\!CH_2\!\!-\!\!C(OH).CH_3$$

$$\downarrow \qquad\qquad\qquad\qquad \downarrow$$

$$(CH_3)_2C\!\!-\!\!\!-\!\!\!-\!\!\!-\!\!CH.COOH \qquad\qquad (CH_3)_2C\!\!-\!\!\!-\!\!\!-\!\!\!-\!\!C.COOH$$
$$|\qquad\qquad\qquad\quad| \qquad\qquad\qquad\qquad |\qquad\qquad\qquad\quad\|$$
$$CH \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_2$$
$$|\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$CH_2.CH:C.CH_3 \qquad\qquad\qquad CH_2.CH_2.C.CH_3$$

α-Cyclogeranic Acid β-Cyclogeranic Acid

The position of the double linkage in the α-series is shown by the fact that, on oxidation, they yield isogeronic acid, which, on further oxidation, is converted into ββ-dimethyl adipic acid, the β-series in the same way being transformed into geronic acid and αα-dimethyl adipic acid, thus :—

α-Series.

$$(CH_3)_2C\text{----}CH.COOH$$
$$\quad | \qquad\qquad |$$
$$CH_2 \quad C.CH_3 \qquad \rightarrow$$
$$\quad | \qquad\quad ||$$
$$CH_2\text{----}CH$$

$$(CH_3)_2C\text{----}CH.COOH$$
$$\quad | \qquad\qquad |$$
$$CH_2 \quad CO.CH_3$$
$$\quad |$$
$$CH_2.COOH$$
$$\qquad\qquad \downarrow$$

$$(CH_3)_2C\text{----}CH_2.COOH$$
$$\quad |$$
$$CH_2 \qquad\qquad \leftarrow$$
$$\quad |$$
$$CH_2.COOH$$

$$(CH_3)_2C\text{---}CH_2.COCH_3$$
$$\quad |$$
$$CH_2$$
$$\quad |$$
$$CH_2.COOH$$

ββ-dimethyl adipic acid

β-Series.

$$(CH_3)_2C\text{----}C.COOH$$
$$\quad | \qquad\quad ||$$
$$CH_2 \quad C.CH_3 \qquad \rightarrow$$
$$\quad | \qquad\quad |$$
$$CH_2\text{----}CH_2$$

$$(CH_3)_2C\text{----}COOH$$
$$\quad |$$
$$CH_2$$
$$\quad |$$
$$CH_2\text{----}CH_2.CO.CH_3$$
$$\qquad\qquad \downarrow$$

$$(CH_3)_2C\text{---}COOH$$
$$\quad |$$
$$CH_2$$
$$\quad |$$
$$CH_2.CH_2.COOH$$

αα-dimethyl adipic acid

One of the most important derivatives of citral is *ionone*, which, in the form of pseudo-ionone $C_{13}H_{20}O$, is formed by the condensation of citral with acetone.

$$\overset{\displaystyle CH_3CO.CH_3}{(CH_3)_2.C:CH.CH_2.CH_2.C(CH_3):CH.CHO. \longrightarrow}$$
$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.CH:CH.CO.CH_3$$
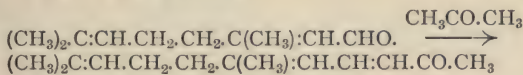
The ψ-ionone, when boiled with dilute sulphuric acid, then passes into α- and β-ionone.

$$CH_2.CH:C(CH_3)_2 \qquad\qquad CH_2 . CH_2 . C(CH_3)_2$$
$$\quad | \qquad\qquad\qquad \rightarrow \qquad | \qquad\qquad |$$
$$CH_2.C(CH_3):CH.CH:CH.COCH_3 \qquad CH:C(CH_3).CH.CH:CH.COCH_3$$

$$\text{and} \quad CH_2.CH_2 . C.(CH_3)_2$$
$$\qquad\qquad | \qquad\qquad |$$
$$\qquad CH_2.C(CH_3):CH.CH:CH.COCH_3$$
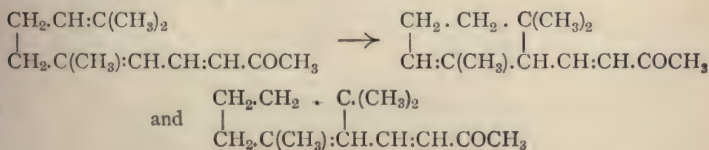
These two isomers are oils which possess a remarkable odoui of violets, and are employed largely in the manufacture of violet essence. Their constitution is determined by the fact that they yield $\beta\beta$ and $\alpha\alpha$ dimethyl adipic acids respectively.

The two isomeric cyclo-citrals are also known, but have to be prepared in an indirect manner, since citral on treatment with acids passes into paracymene, so that for their preparation citral is shaken with cyanoacetic acid in the presence of sodium hydroxide, and the resulting citrylidenecyanacetic acid converted into the derivative corresponding to cyclo-citral by the action of acids. On hydrolysis of the cyclic compounds with alkali, the corresponding cyclo-citrals are obtained, thus the formation of β-cyclocitrals may be shown.

$$
\begin{array}{c}
CH_2.CH:C(CH_3)_2 \\
|\\
CH_2.C(CH_3):CH.CH:C(CN).COOH
\end{array}
\longrightarrow
\begin{array}{c}
CH_2.CH_2 \ . \ C(CH_3)_2 \\
| \qquad\qquad | \\
CH_2.C(CH_3):C.CH:C(CN).COOH \\
\downarrow \\
CH_2 . CH_2 . C(CH_3)_2 \\
| \qquad\qquad | \\
CH_2.C(CH_3):C.CHO
\end{array}
$$
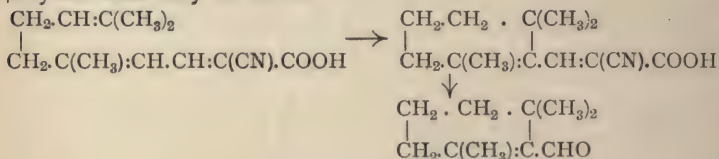
These cyclo-citrals readily oxidize to the corresponding cyclo-geranic acid. β-cyclo-cital, alone is known in a state of purity. It condenses directly with acetone to form β-ionone. The reduction of citral by sodium amalgam converts it into *geraniol* $C_{10}H_{17}OH$, an alcohol found in many essential oils, from which it may be isolated by conversion into the characteristic calcium chloride compound $C_{10}H_{18}O.CaCl_2$. Its constitution follows from its relationship to citral and to geranic acid, into which it readily passes on oxidation. Acetic acid, containing a small quantity of sulphuric acid, converts it into terpineol, whilst if it be shaken with a 5 % solution of sulphuric acid alone, it yields terpin hydrate.

Terpineol   Terpin hydrate
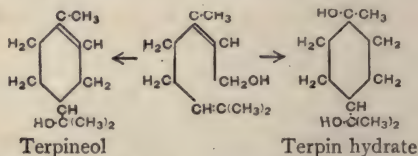
When geraniol is heated with potassium bisulphate to 170° C., it loses water, and yields the hydrocarbon $C_{10}H_{16}$ (anhydro-

geraniol), which was the first olefine terpene to be prepared.   By the action of hydrochloric acid on geraniol a mixture of chlorides is obtained, and these, on digestion with alcoholic potash, yield the inactive modification of another olefine terpene alcohol, known as *linalool*, $C_{10}H_{17}OH$.   The *d*-form of this alcohol is found in coriander oil, and the *l*-form in oil of linaloes.   It is also formed when a faintly alkaline solution of acid geranyl phthalate is distilled in a current of steam.   It is most probable that it corresponds to the structural formula—

$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3)(OH)CH:CH_2,$$
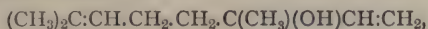
which accounts for its optical activity by the presence of an asymmetric carbon atom, and for the extreme readiness with which it passes into methylheptenone on oxidation, a fact necessitating the presence of a grouping

$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):.$$
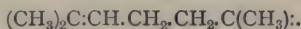
The alternative formulæ proposed by Barbier and Bouveault, namely,

$$(CH_3)_2.C:CH.CH_2.CH_2.CH(CH_3).C(OH):CH_2 \text{ and}$$
$$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH:CH.OH,$$
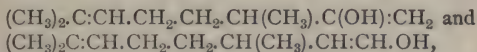
representing the enolic forms of an unsaturated methyl ketone and an aldehyde (citronellal).

Of the other aldehydes of the olefine terpene series which have been described, *citronellal* $C_{10}H_{18}O$, and *rhodinal* $C_{10}H_{18}O$, are the more important.   Citronellal was first obtained by F. Dodge from citronella oil.   It is a dextro-rotatory liquid and shows the usual aldehydic properties.   On reduction it is converted into the corresponding alcohol citronellol.   A considerable amount of controversy has taken place as to the structure of this aldehyde and its derivatives, and the matter can hardly be said to be definitely decided at the present time.   Tiemann and Schmidt considered, from a study of the decomposition of the aldehyde, that it was a substance of the following structure :—

$$\overset{1}{C}H_3.\overset{2}{C}:\overset{3}{C}H.\overset{4}{C}H_2.\overset{5}{C}H_2.\overset{6}{C}H.\overset{7}{C}H_2.\overset{8}{C}HO,$$
$$\quad\;\; |\qquad\qquad\quad |$$
$$\quad\;\; CH_3\qquad\qquad CH_3$$
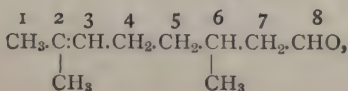
because, on reduction to the alcohol, the latter on oxidation with potassium permanganate, was converted into acetone and β-methyl adipic acid $HOOC.CH_2.CH_2.CH(CH_3).CH_2.COOH$, a result requiring the double linkage to be between the carbon atoms 2 and 3, and a methyl group at 5 or 6. Position 6 was decided upon for the methyl group, because citronellal and acetic anhydride condensed together to form a cyclic alcohol, which was assumed to be isopulegol
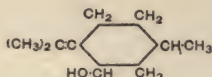
showing that the carbonyl group in the aldehyde was in the *meta*-position to the $> CH.CH_3$ group. Later work has, however, shown that the above constitutional formula of isopulegol is not quite correct. Barbier and Bouveault, on the other hand, are of the opinion that citronellal is to be represented thus :—

$$CH_3.C.CH_2.CH_2.CH_2.CH.CH_2.CHO.$$
$$\overset{\|}{CH_2} \qquad \overset{|}{CH_3}$$
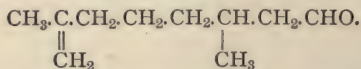
and that Tiemann's formula represents the isomeric rhodinal. As arguments in favour of their view they point out that although the physical properties of rhodinol and citronellol are almost identical, and although drastic oxidation yields acetone and β-methyl adipic acid in the case of both alcohols, a limited oxidation, on the other hand, in the case of rhodinol, yields a mixture of rhodinal and menthone and an acid, rhodinic acid $C_{10}H_{18}O_2$. Again, rhodinal-oxime, on treatment with acetic anhydride, is spontaneously transformed into menthone, whilst the oxime of citronellal yields only the corresponding nitrile. Thus rhodinal would appear to be—

Rhodinal   Menthone
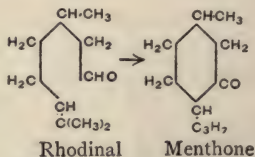
They also pointed out that the derivatives of rhodinal and citronellal possessed different physical constants, an argument

objected to by Tiemann on the grounds that Barbier and Bouveault were working with mixtures and not definite compounds. Further confirmation of Barbier and Bouveault's views was apparently obtained by Harries and Schauwecker, who found that citronellal yielded a dimethylacetal, which, on oxidation with potassium permanganate, was converted into the corresponding glycol derivative.

$$C_{10}H_{18}O \rightarrow C_{10}H_{18}(OCH_3)_2$$

$$\downarrow O$$

$$CH_3.C(OH).CH_2.CH_2.CH_2.CH.CH_2.CH(OCH_3)_2$$

$$| \qquad\qquad\qquad\qquad |$$

$$CH_2OH \qquad\qquad\qquad CH_3$$
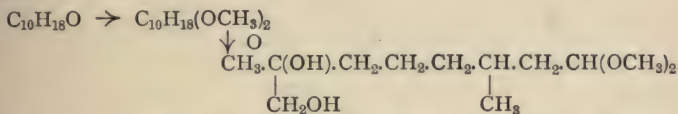
This was assumed to possess the above constitution, since on further oxidation by chromic acid it yielded a keto-aldehyde.

$$CH_3.CO.CH_2.CH_2.CH_2.CH(CH_3).CH_2.CHO$$
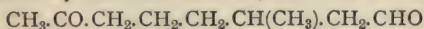
They also found that the citronellaldimethylacetal could be further oxidized by potassium permanganate in acetone solution to acetone and the acetal of an aldehyde acid, which on hydrolysis was found to be the semi-aldehyde of β-methyl adipic acid, the latter reaction being easily explained by the Tiemann formula.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C\!:\!CH.CH_2CH_2.CH(CH_3).CH_2.CH(OCH_3)_2 \rightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CO$$

$$+\; HOOC.CH_2.CH_2.CH(CH_3)_3CH_2.CH(OCH_3)_2$$
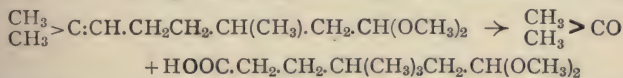
More recently Harries has tried to settle the question definitely by a study of the action of ozone on citronellal and its derivatives. Thus, if the Barbier and Bouveault formula were correct, the ozonide should decompose into formaldehyde and a compound of nine carbon atoms containing a $>CO$ group at the position of the double bond, but all the ozonides, with the exception of citronellal ozonide, yielded on decomposition with water a mixture of equivalent quantities of acetone peroxide and β-methyl adipic acid. From a consideration of these complex results Harries concludes that the citronellal derivatives are mixtures of the two different types, the portion of the mixture of the citronellic (Barbier) type being the more unstable, as the terminal oxygenated group becomes more acidic in character.

Rhodinol, $C_{10}H_{19}OH$. The *l*-form of this alcohol is found in the essences of geranium and of rose. The inactive variety has

been prepared by Barbier and Bouveault by the reduction of synthetic geranic acid (see p. 41) with alcohol and sodium, or the geranic acid may be reduced by sodium, in amyl alcohol solution to i-rhodinic acid, the ester of which, on reduction with sodium and ethyl alcohol, yields i-rhodinol
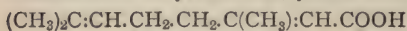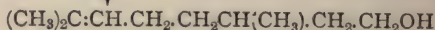
$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.COOH$$
<center>Geranic acid</center>
<center>↓</center>
$$(CH_3)_2C:CH.CH_2.CH_2CH(CH_3).CH_2.CH_2OH$$
<center>Rhodinol</center>

Before passing to the consideration of the cyclic terpenes, mention might be made of an isomer of ionone, namely, *irone* $C_{13}H_{20}O$, the odoriferous principal of the iris root. It is a colourless liquid which boils at 144°C. (16 mm.). The constitution of this cyclic ketone has been determined by Tiemann and Krüger in the following manner. Irone, when heated with hydriodic acid and phosphorus, yields the hydrocarbon *irene* $C_{13}H_8$, oxidation of the latter compound then yielding a number of degradation products of the empirical formula $C_{13}H_{16}O_3$, $C_{13}H_{14}O_5$, $C_{13}H_{12}O_7$, and $C_{12}H_{12}O_6$, known respectively as trioxydehydroirene, iregenondicarboxylic acid, iregenontricarboxylic acid, and ioniregentricarboxylic acid. The distillation of the ammonium salt of the last-named acid gives rise to an imide acid, the silver salt of which, when heated, is transformed into dimethylhomophthalimide, thus :—

$$C_{12}H_{12}O_6=C_9H_9(COOH)_3 \rightarrow \overset{(CO)_2NH}{\underset{COOH}{|\atop C_9H_9}} \rightarrow CO_2 + \overset{(CH_3)_2C\text{———}CO}{\underset{CO\text{———}NH}{|\quad\quad|\atop C_6H_4}}$$
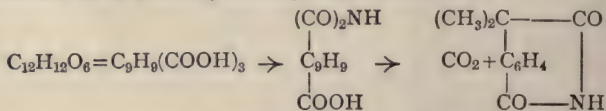
From these results it may be deduced that irone is in all probability a trimethyltetrahydrocinnamenyl methyl ketone of the following structure :—
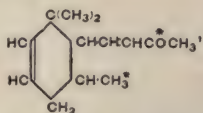
If this be so, the effect of the hydriodic acid is to convert the ketone into a naphthalene derivative by loss of water at *,
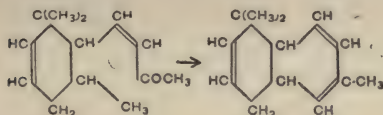
oxidation then taking place and transforming this hydrocarbon first into a dehydro-irene and then further into an hydroxy-acid. This acid lactonizes readily, so that, instead of the free acid, the lactone $C_{13}H_{16}O_3$ or trioxydehydroirene is obtained.
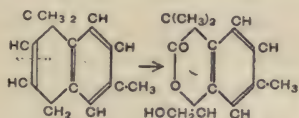
The subsequent stages of the formation of the dimethylhomophthalimide are shown in the following scheme :—
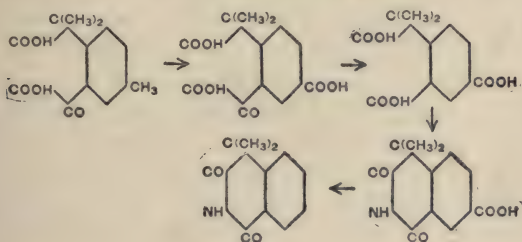
Cyclic Terpenes—The chief sources of the terpenes, and their naturally occurring derivatives are the essential oils obtained from various plants belonging for the most part to the natural order of the Coniferæ. Many of these oils, *e.g.* turpentine, oil of citron, orange oil, and oil of thyme, consist chiefly of hydrocarbons, whilst others, such as oil of camphor, caraway oil, thuja oil, oil of peppermint, etc., contain oxygen-holding compounds mainly of an alcoholic or ketonic nature. The products obtained as oils from the various plants either by extraction by pressure, by solvents, or by distillation in a current of steam are in the case of the hydrocarbons for the most part substances of the empirical

formula $C_{10}H_{16}$, and which have approximately equal boiling-points, ranging from 160-190° C. On this account it is almost impossible to separate the hydrocarbons by fractional distillation, so that in order to prepare individual members of the series it is necessary to obtain a series of crystalline derivatives. These may be separated from one another by taking advantage of their varying physical properties, and the separate members may then be converted into terpenes again.

With the exception of camphene, all the terpenes are liquids at ordinary temperature. They possess a characteristic odour, are fairly stable towards alkalis, but as a rule undergo decomposition when subjected to the action of acids. Many resinify rapidly on exposure to air. They are characterized by the formation of addition compounds with the halogens or halogen halides, and as Tilden has shown, form well-defined compounds with nitrosyl chloride. Baeyer regards these latter compounds not as simple addition products, but considers them to be bimolecular compounds, the nitrosochloride of limonene being represented, for example, as $C_{10}H_{16}(Cl) - N_2O_2 - (Cl)C_{10}H_{16}$.

The terpenes may be sub-divided into two groups, the *monocyclic terpenes* and *camphors*, which may be considered as reduced cymene derivatives, since many of them can be converted into cymene or its derivatives by relatively simple reactions; and the more complex (usually *bi-cyclic*) terpenes.

The monocyclic terpenes are shown by their reactions, as mentioned above, to contain a nucleus of six carbon atoms, and as many of them yield terephthalic acid on oxidation, it may be concluded that they possess two side chains, usually in para-positions, these chains consisting generally of a methyl group and the grouping $- C\begin{smallmatrix} \diagup C\ - \\ \diagdown C\ - \end{smallmatrix}$. They are also unsaturated, and contain two double bonds in the molecule, since they form dihydrochlorides, tetrabromides, bisnitrosochlorides, etc. These double bonds may be either both in the nucleus, or one in the side chain and one in the nucleus. Semmler has also shown that a division of the terpenes may also be made into (1) those

possessing a methyl group in the side chain with a double bond in the nucleus, and (2) those in which a second double bond connects the group $-\, C \begin{smallmatrix} \diagup C\, - \\[2pt] \diagdown C\, - \end{smallmatrix}$ to the nucleus, or may be contained in this group. The former he designates as *ortho-terpenes*, the latter as *pseudo-terpenes*, thus :—
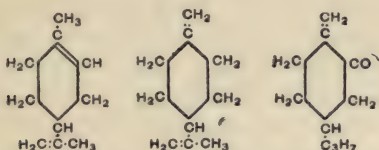
ortho-limonene *pseudo*-limonene *pseudo*-carvone

A convenient system of nomenclature for the monocyclic terpenes has been devised by Wagner, who considers them as all derived from the saturated cyclic hydrocarbon $C_{10}H_{20}$, namely, p-methylisopropylhexamethylene, which he designates as *menthane*, the hydrocarbons $C_{10}H_{16}$ thus becoming *menthadienes*. The carbon atoms in the nucleus are then numbered in accordance with the following scheme :—
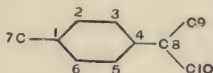
Baeyer, as an alternative, advocates the use of the terms *terpane* and *terpadiene*. The position of the double linkage in the unsaturated members of the series is shown by the use of the symbol Δ followed by a numeral indicating the carbon atom immediately preceding the double bond, the numeral being enclosed in a bracket when the double bond is in the side chain; thus—
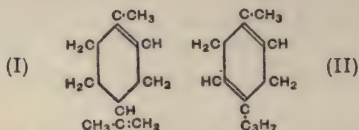
(I) is Δ 1.8(9)-menthadiene, and (II) is Δ.1.4 menthadiene.

The parent hydrocarbon of the group (hexahydro-p-cymene) has been synthesized recently by W. H. Perkin by the application of the Grignard reaction to ethylhexahydro-p-toluate, which leads to the formation of p-menthanol. The alchohol loses water when subjected to the action of potassium hydrogen sulphate and is converted into Δ.8(9) menthene, from which the hydrobromic acid addition product is then formed, and this on reduction with zinc dust and acetic acid yields p-menthane.
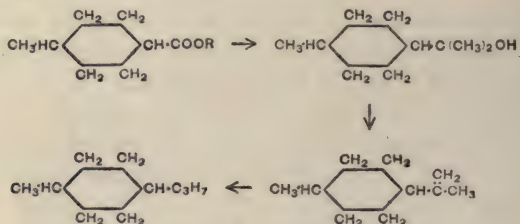
Many attempts have been made from time to time to synthesize the naturally occurring terpenes, but until recent years these were quite unsuccessful ; now, however, owing to the ingenuity of W. H. Perkin and his collaborators, and others, particularly Wallach, Semmler, and Harries, several members of the series have been prepared. As examples of Perkin's method the syntheses of dipentene and carvestrene may be described. In the former case, it was found that cyanacetic ester readily condensed with β-iodopropionic ester to form γ-cyanopentane tricarboxylic ester, which on hydrolysis with hydrochloric acid was converted into pentane-$\alpha\gamma\epsilon$-tricarboxylic acid. By digestion of this acid with acetic anhydride and subsequent distillation, ring formation takes place, and δ-ketohexahydrobenzoic acid is formed.

$CH_2.CN.COOR + 2CH_2I.CH_2.COOR$
$$= 2HI + ROOC.C(CN)(CH_2.CH_2.COOR)_2$$
$$\downarrow$$

$$\begin{array}{l} CH_2.CH_2.COOH \\ HOOC.CH \\ CH_2.CH_2.COOH \end{array} \qquad \leftarrow \qquad (HOOC)_2.C(CH_2.CH_2.COOH)_3$$

$$\downarrow$$

$$\begin{array}{l} CH_2 - CH_2 \\ HOOC.CH \quad CO + CO_2 + H_2O \\ CH_2 - CH_2 \end{array}$$
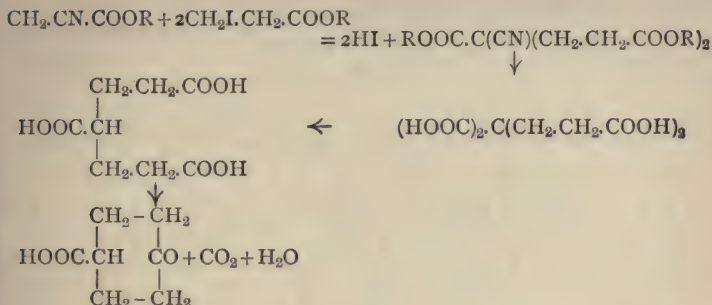
The ester of this acid on treatment with the Grignard reagent is then converted into δ-hydroxyhexahydro-*p*-toluic acid, and this acid on treatment with fuming hydrobromic acid yields the corresponding bromo-derivative. On digestion of this bromo-compound with pyridine, hydrobromic acid is removed and Δ.3-tetrahydro-*p*-toluic acid is formed, the ester of which on treatment with an excess of an ether solution of the Grignard reagent and then with dilute hydrochloric acid yields terpineol. Terpineol, when treated with potassium hydrogen sulphate, is converted into dipentene.

Dipentene   Terpineol
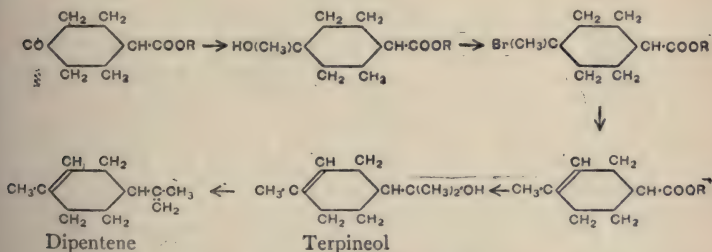
For the preparation of carvestrene the starting-point was *m*-hydroxybenzoic acid, which was reduced to cyclohexanol-3-carboxylic acid, and the latter then oxidized to the corresponding cyclohexanone carboxylic acid, and the process as shown from δ-ketohexahydrobenzoic acid above was repeated, giving finally the hydrocarbon required.
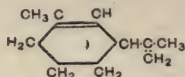
The yield of the cyclohexanone carboxylic acid obtained was unsatisfactory, and Perkin in 1909 tried to improve it by adopting the following method, but again without very satisfactory results. Ethyl oxaladipate, when distilled, yields butane $\alpha\delta\delta$-tricarboxylic ester, the sodium derivative of which may be condensed with ethyl bromo-acetate to form pentane-$\alpha\delta\delta\epsilon$-tetra-carboxylate. This ester was then hydrolyzed, and the free acid heated until evolution of carbon dioxide ceased, when pentane-$\alpha\delta\epsilon$-tricarboxylic acid was formed. Esterification of the acid and subsequent heating with sodium transformed it into ethyl cyclo-hexanone-3.6-dicarboxylate, from which by hydrolysis and elimination of carbon dioxide, cyclohexanone-3-carboxylic acid was ultimately obtained.

$$ROOC.CO.CH(COOR).(CH_2)_3.COOR \rightarrow CH(COOR)_2.(CH_2)_3.COOR + CO$$
$$\downarrow CH_2Br.COOR$$
$$ROOC.CH_2.C(COOR)_2.(CH_2)_3.COOR$$
$$\text{Hydrolysis} \downarrow \text{Heat}$$
$$HOOC.CH_2.CH(COOH).(CH_2)_3.COOH$$
$$\downarrow$$
$$ROOC.CH_2.CH(COOR).(CH_2)_3.COOR$$
$$\downarrow Na$$

$$\begin{array}{ccc}
CH_2.CH_2 & & CH_2.CH_2 \\
| \quad | & & | \quad | \\
CH_2 \ CH.COOR & \leftarrow & ROOC.CH \ CH.COOR \\
| \quad | & & | \quad | \\
CO. \ CH_2 & & CO.CH_2 \\
\end{array}$$
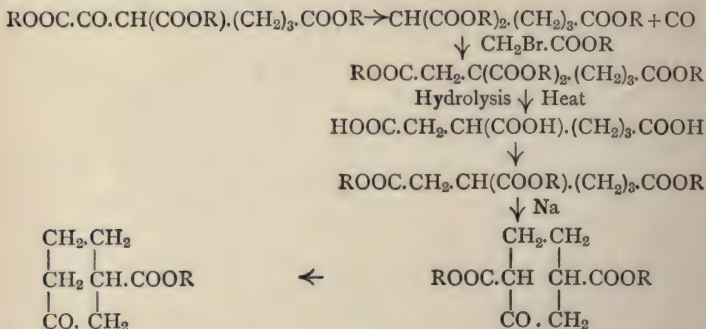
By a similar process a series of menthenols, menthadienes, menthanols, and menthanes have been obtained, starting from partially reduced toluic acids.

Various hydrocarbons of the monocyclic terpene series have been synthesized by other processes from open chain and other compounds, a resumé of some of the more important methods being here given. Thus Wallach has shown that 1.4-methylcyclo-hexanone, which can be prepared from α-hydroxyhexahydro-*p*-

toluic acid, condenses with ethyl-α-bromoisobutyrate in the presence of zinc to form a cyclic hydroxy-ester, and this latter compound on hydrolysis, and subsequent heating loses carbon dioxide and passes into $i.\Delta.4(8)$-menthene. The hydrocarbon so obtained, when boiled with dilute sulphuric acid, isomerizes to $\Delta.3$-menthene.

i-Δ.3.menthene i.Δ4(8).menthene
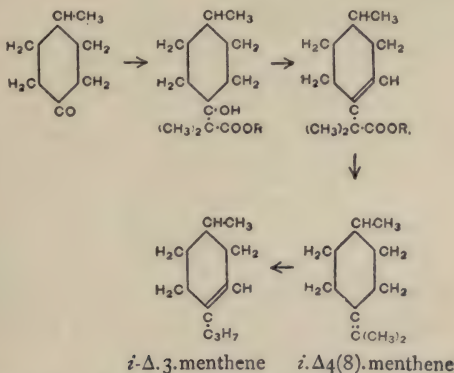
It was found that the hydroxy-esters, such as those mentioned above, are only hydrolyzed with difficulty by caustic alkali, decomposition taking place with the formation of compounds of the type shown as under :—

$$R : C(OH).R^{11}.COOH \rightarrow R : CO + R^{11}H.COOH$$
$$HOH$$
$$R : C(OH).R^{11}.COOH \rightarrow R : C(OH)H + R^{11}(OH).COOH,$$
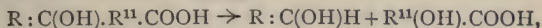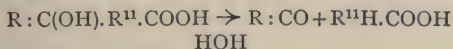
but the esters formed by unsaturated acids are more easily hydrolyzed.

Δ.3-menthene may also be prepared by the xanthogenic ester process from menthol, and since this alcohol may be obtained from citronellal, a complete terpene synthesis is obtained from an open chain compound. In this process citronellal is converted into isopulegol by the action of acetic anhydride, and the alcohol oxidised to isopulegone, which is then transformed into pulegone by baryta water. The reduction of pulegone hydrobromide yields menthone, further reduction by sodium and alcohol leading to the formation of menthol.

Citronellal Isopulegol Isopulegone Pulegone

Menthene-3 Menthol Menthone
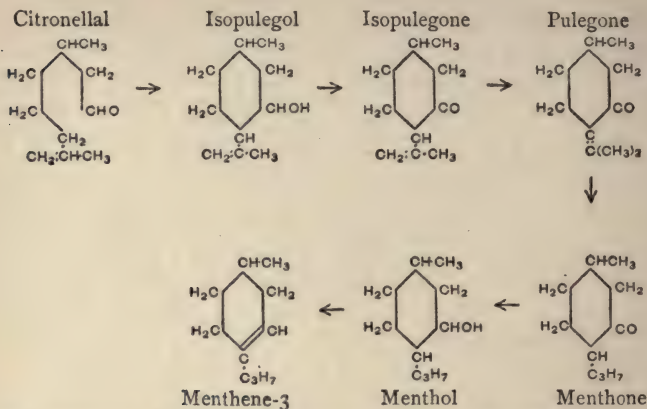
As menthone has been synthetically prepared in various other ways (see p. 71), one has numerous syntheses of menthene-3.

α-Phellandrene can now be considered as a synthetic hydrocarbon, since terpineol, which was artificially prepared by Perkin, yields a nitrosochloride, and this, by the action of sodium ethoxide, is converted into hydroxydihydrocarvoxime. The oxime on hydrolysis yielded *i*-carvone. Carvone hydrobromide was reduced to Δ-6.menthenone-2, and Harries showed that phosphorus pentachloride converted the latter ketone into 2-chloro-α-phellandrene, from which α-phellandrene was obtained by boiling with zinc dust and methyl alcohol.

Terpineol nitrosochloride   *i*-carvone

1-phellandrene   2-choro-α-phellandrene
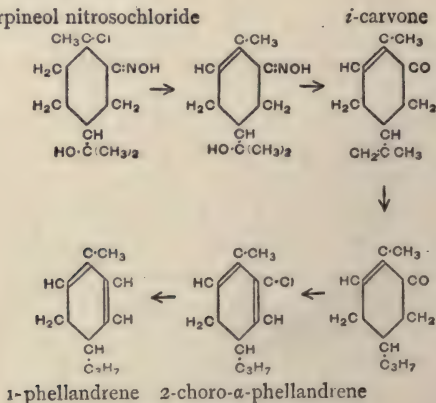
Better results are obtained in this latter case if Δ-6-menthenone-2 is converted into its oxime, the oxime reduced to the amine, and the amine distilled under reduced pressure with phosphoric acid.
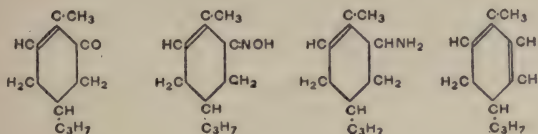
Synthetic terpineol, in presence of 5 per cent. sulphuric acid, passes into terpin hydrate, and terpin hydrate, when boiled with a diluted sulphuric acid (2 : 1), loses water and gives rise to several products, among which is found the hydrocarbon terpinene.

Terpineol		Terpin hydrate		Terpinene
$C_{10}H_{18}O$	$\longrightarrow$	$C_{10}H_{18}(OH)_2$	$\longrightarrow$	$C_{10}H_{16}$
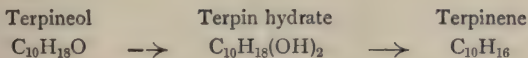
This hydrocarbon terpinene may exist in three isomeric forms, known as the α, β, and γ-terpinenes, which possess the following structures :—
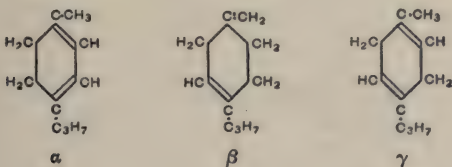
and a hydrocarbon practically identical with the α-form has been recently synthesized by Auwers and Hessenland in the following manner. Chloroform and o-cresol condense in the presence of caustic alkali to form 2-methyl-2-dichloromethyl-1-ketodihydrobenzene, which reacts with magnesium isopropyl iodide to form a ketone of the structure shown in (I).

(I)
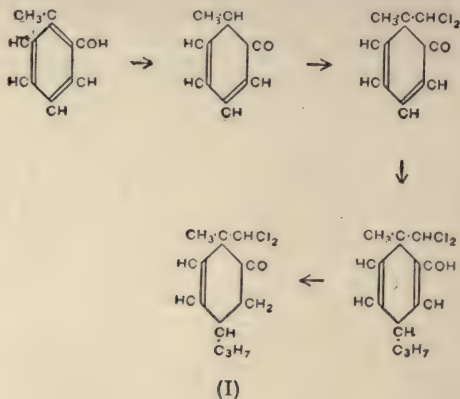
This ketone in contact with sulphuric acid isomerizes to one of the structure shown in (II), and is then reduced to the cyclohexenone (III) by zinc and acetic acid.

(II)   (III)   (IV)
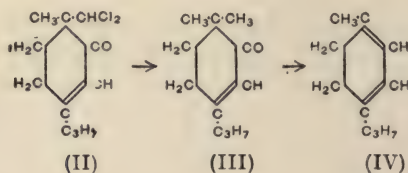
Finally, the cyclohexenone, under the influence of hot alcoholic potash, passes into the hydrocarbon (IV) identical in almost all respects with α-terpinene.

Terpinolene may also be included among the synthetic terpenes, since it can be obtained from dipentene, the dihydrobromide of which by bromination is converted into tribromo-1.4.8-menthane. The latter, on reduction with zinc and glacial acetic acid, yields the acetate of Δ.4(8)-menthenol, and by boiling this with quinoline Baeyer obtained terpinolene.
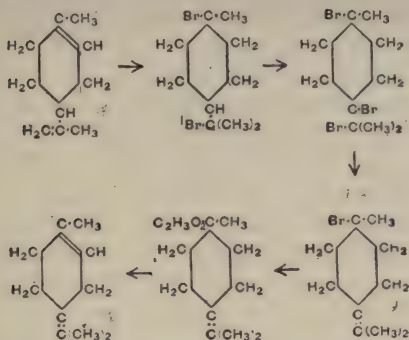
The relationships of these terpenes may be illustrated by means of the following chart :—

Pentane-$\alpha\gamma\epsilon$-tricarboxylic acid

$\downarrow$

δ-ketohexahydrobenzoic acid

$\downarrow$

δ-hydroxyhexahydro-p-toluic acid

$\downarrow$

$\Delta.3$-tetrahydro-p-toluic acid

$\downarrow$

Terpineol

Terpin   Dipentene $\rightarrow$ carvone $\rightarrow$ α-phellandrene

Terpinene   Terpinolene

l-Rhodinal $\leftarrow$ Menthone

$\downarrow$

Menthol $\leftarrow$ citronellal

Menthyl chloride   Methyl cyclohexanone-1.4.

p-menthane $\Delta.3$-menthene $\leftarrow$ $\Delta.4(8)$ menthene
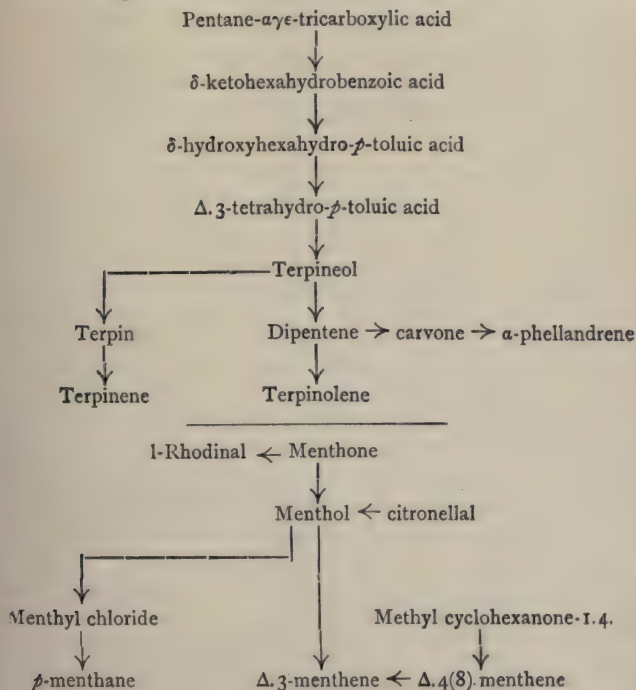
To consider these hydrocarbons in slightly more detail it may be observed that *dipentene* is the optically inactive form of *limonene*. It is found in many essential oils and is a product of the action of high temperatures on many terpenes (pinene, camphene, etc.). It is also formed when linalool is heated with formic acid. The dipentene obtained by these methods is more or less impure, and Wallach has shown that, in order to obtain the pure hydrocarbon it is best to heat the dihydrochloride with anhydrous sodium acetate and glacial acetic acid and distil the product in a current of steam, the oily distillate being further heated with potassium hydroxide, redistilled in steam, and finally fractionated. The active *d*-limonene is best prepared from oil of orange rind, or from caraway oil, by fractionation ; the *l*-variety from oil of fir-cones, or synthetically by the xanthogenic ester method from dihydrocarveol (p. 76). Dry hydrochloric acid converts both forms into the active limonene hydrochlorides, but in the presence of water both forms give the inactive dipentene dihydrochloride. The nitroso chlorides exist in four optically active modifications, two corresponding to each form of limonene, and known respectively as the α and β-forms. These isomers may in each case be separated by digestion with cold chloroform, the β-form being insoluble in the solvent. When heated with alcoholic potash they pass by loss of hydrochloric acid into the corresponding *d* and *l*-carvoximes.
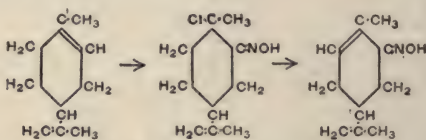
Again these nitrosochlorides condense readily with organic bases to yield nitrolamines of the type $C_{10}H_{15}(:NOH).NHR$.

The constitution of dipentene (and of limonene) has been definitely settled by the synthesis of the hydrocarbon by Perkin's method, although Wallach had earlier arrived at a similar conclusion by a study of the oxidation products of terpineol. Thus wit as found that terpineol, on oxidation with chromic acid, gave

rise to a keto-lactone $C_{10}H_{16}O_3$, which on further oxidation was decomposed into terpenylic acid (a lactonic acid) and acetic acid, a result which precludes the hydroxyl group in terpineol from being in any other position than in the side chain, thus :—
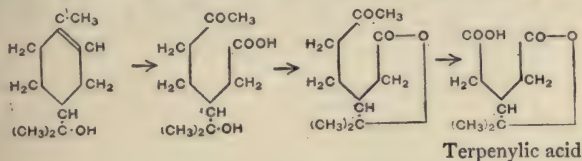
Terpenylic acid

Further support for this terpineol formula was also given by Tiemann and Semmler, who showed that on oxidation with chromic acid the above keto-lactone was converted into homoterpenylic acid,
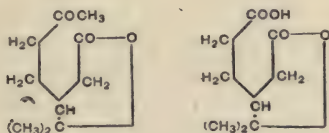
the presence of the $CH_3.CO-$ group being shown by the formation of bromoform or carbon tetrabromide when the keto-lactone was treated with bromine and sodium hydroxide. Thus, knowing the constitution of terpineol, that of limonene and dipentene follows by elimination of water from positions 8 and 10. *Terpinene* is found in cardamom oil and in oil of marjoram, and is formed by the action of alcoholic sulphuric acid on many terpenes or terpene derivatives. Since it may be prepared by the action of concentrated sulphuric acid on terpineol and is inactive, three possibilities arise, and the hydrocarbon may be represented as

α   β   γ
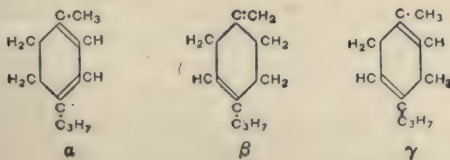
β-terpinene has been synthesized by Wallach by the condensation of sabina-ketone (I) with bromoacetic ester in the presence of zinc. The sabinol acetic ester (II) is heated with acetic anhydride and the product hydrolyzed when an unsaturated acid is produced, from which by elimination of carbon dioxide a hydrocarbon identical with β-terpinene is obtained.
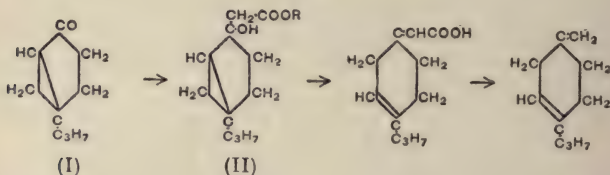
On oxidation this hydrocarbon does not give rise to any of the known products of oxidation of ordinary terpinene, so that β-terpinene cannot be considered as a constituent of ordinary terpinene. The α-terpinene obtained by Auwers (p. 58) yields a nitrosite which melts at the same temperature as that of Wallach's α-terpinene. Crude terpinene on oxidation yields an acid identical with αα¹-dihydroxy-α-methyl-α¹-isopropyl adipic acid, and Auwers' hydrocarbon yields the inactive form of this acid. The crude terpinene is thus probably a mixture of the α and γ forms, but the matter cannot as yet be considered as definitely decided.

Phellandrene—The naturally occurring phellandrene is a mixture of two isomers, viz. α-phellandrene (Δ.1.5-menthadiene) and Δ2:1(7) menthadiene or β-phellandrene.
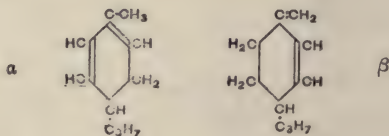
as was shown by Semmler, who found that crude phellandrene on oxidation with potassium permanganate was converted into a

mixture of two hydroxy-acids, which on further oxidation with lead peroxide yielded respectively l-isopropyl succinic acid and l-α-isopropyl glutaric acid thus :—

$$
\begin{array}{ccc}
\mathrm{CH(CH_3)_2} & & \mathrm{CH(CH_3)_2} \\
| & & | \\
\mathrm{CH_2.CH.CHOH} & \rightarrow & \mathrm{CH_2.CH.COOH} \\
| \qquad\quad | & & | \\
\mathrm{COOH\ \ COOH} & & \mathrm{COOH} \\
\quad (\mathrm{I}) & &
\end{array}
$$

$$
\begin{array}{ccc}
 & & \mathrm{CH(CH_3)_2} \\
 & & | \\
\mathrm{CH(CH_3)_2} & & \mathrm{CH_2.CH.CHOH} \\
| & & | \qquad\quad | \\
\mathrm{CH_2.CH.COOH} & \leftarrow & \qquad \mathrm{COOH} \\
| & & \mathrm{CH_2.COOH} \\
\mathrm{CH_2.COOH} & & \quad (\mathrm{II})
\end{array}
$$
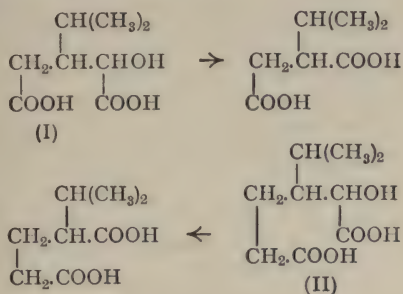
and since it was also shown that the hydroxy-acid (II) could not be oxidized to (I) by potassium permanganate, it follows that the simultaneous production of the two acids in the oxidation of phellandrene must arise from the occurrence of two isomeric hydrocarbons in the crude terpene. The formation of the hydroxy-acid shows that a double bond necessitating the grouping – CH:CH – must exist in the molecule, and since the molecular refraction indicates a second double bond, this can only be of necessity between positions 1 and 6, or 1 and 7, in order to allow of the formation of the above acids. Further observations of Wallach have led to the conclusions that the phellandrene of elemi and fennel is a δ-α-phellandrene, the one obtained from Australian eucalyptus, being the corresponding l-compound, whilst water-fennel yields δ-β-phellandrene.

The oxidation of α-phellandrene by nitric acid gives a compound $C_{10}H_{15}N_3O_6$, which on reduction yields an unstable diaminocymene, and since the hydrochloride of this base is oxidized by ferric chloride to thymo-quinone, it must be a δ-diaminocymene. These reactions may be explained in the following manner :—
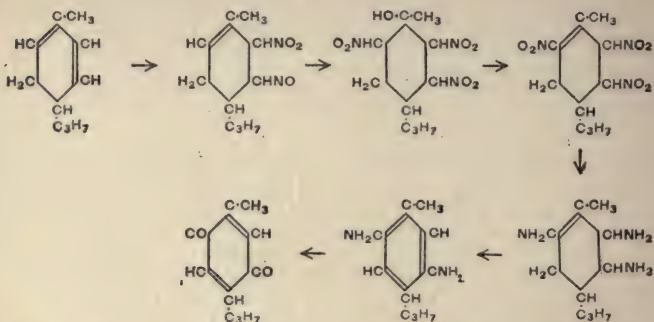
The position of one double bond in α-phellandrene is also shown by its conversion into carvothujone (or carvotanacetone), of which the constitution is known. This conversion is brought about by the transformation of phellandrene nitrosite into α-nitrophellandrene by the action of alcoholic potash, reduction of the nitro compound with zinc dust and acetic acid, then giving the ketone, thus :—

Carvothujone
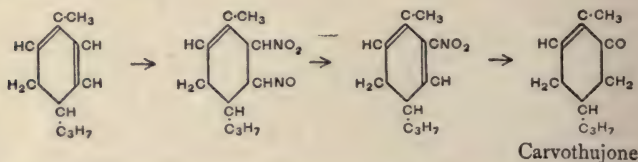
Oxygen Derivatives of Monocyclic Terpenes—The genetic relationships and chief decomposition products of these compounds are illustrated in the following diagrams :—

Dipentene (limonene)
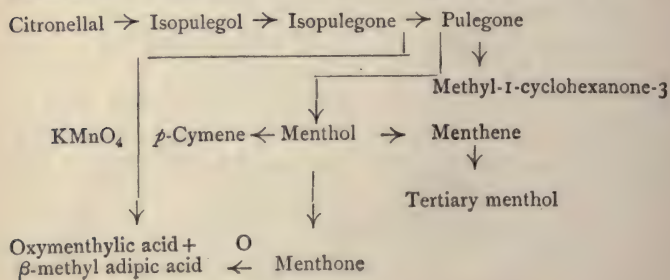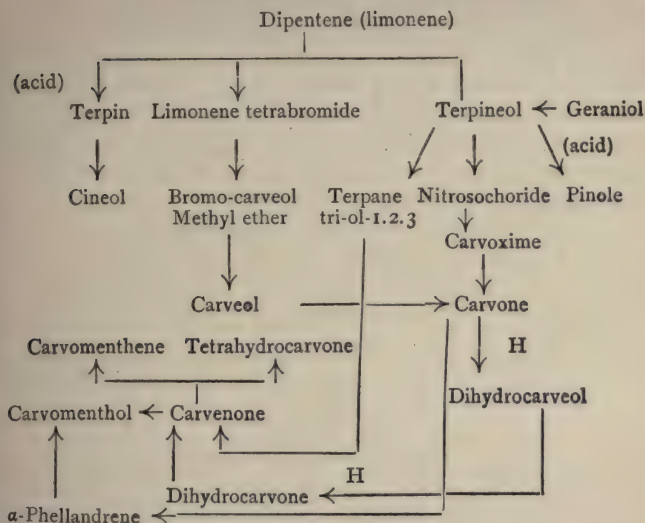
Among the alcohols of this series, p-menthol, terpin, and terpineol may be considered as the more important. Ordinary menthol is a secondary alcohol, the l-variety being the chief constituent of oil of peppermint. This form has been obtained synthetically from pulegone, by converting the hydrobromide into menthone, the reduction of which by sodium and alcohol yields l-menthol.
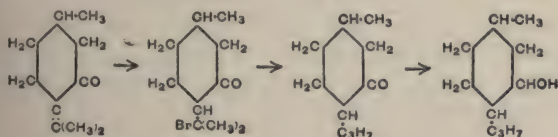
By the reduction of ordinary menthone, a mixture is obtained from which on benzoylation a liquid d-menthol benzoate may be separated, and this on hydrolysis yields d-menthol. This variety has $[\alpha]_D = +2.03$, whilst Kondakow, by reduction of the l-mentheon of Bucco leaves with sodium and methyl alcohol, has obtained a d-menthol with $[\alpha]_D = +32°.37'$. On oxidation with

5

chromic acid, menthol is converted into the ketone, menthone, whilst if potassium permanganate be used, oxymenthylic acid, $C_{10}H_{18}O_3$, β-methyl adipic acid, $C_7H_{12}O_4$, carbon dioxide, and other fatty acids are formed. Hydriodic acid at high temperatures reduces menthol to p-cymene. The constitution of menthol is determined from that of menthone (q.v.). A *tertiary-p-menthol* (p-menthanol-4) has been synthesized by Perkin by the following process. α-Bromohexahydro-p-toluic acid is converted by the action of sodium carbonate into Δ.1-tetrahydro-p-toluic acid and α-hydroxyhexahydro-p-toluic acid, the latter acid, on treatment with sulphuric acid, yielding methyl-1-cyclohexanone-4, from which by treatment with magnesium isopropyl iodide and subsequent hydrolysis, tertiary-p-menthol is obtained.
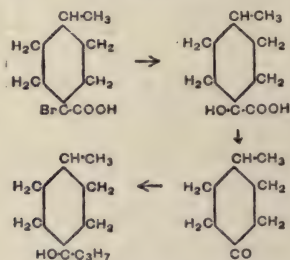
This menthol when heated with potassium bisulphate loses water and passes into *i*-menthene

Terpin, $C_{10}H_{18}(OH)_2$, is a p-menthane-diol-1.8. Two stereo-isomeric forms of this alcohol are known, viz., *cis*-terpin and *trans*-terpin. The latter modification is anhydrous and is formed by the addition of silver acetate to a glacial acetic acid solution of dipentene dihydrochloride. The precipitated silver halide is filtered off, the acid solution neutralized and extracted with ether, and the acetyl derivative so obtained, then hydrolysed, with caustic alkali. It melts at 156° C. The *cis*-compound, melting at 104° C., is obtained by heating terpin hydrate, the synthesis of which was accomplished by Perkin by the action of dilute sulphuric acid on synthetic terpineol (see p. 53), a reaction proving the alcohol to be a menthane di-ol.

Terpineol → Terpin
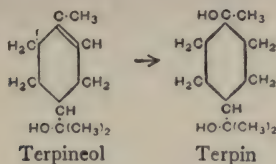
Terpin hydrate is also obtained synthetically by the action of formic acid on linalool and on geraniol, a reaction which points to it being an alcohol of the fatty series. This result is in direct accordance with the formation of the hydrate from terpin itself, if it be considered that the hexamethylene ring is broken between the carbon atoms 3 and 4 and the elements of water then added.

$(CH_3)_2.C:CH.CH_2.CH_2.C(OH).CH:CH_2$
    $\overset{|}{CH_3}$
    Linalool

$(CH_3)_2.C:CH.CH_2.CH_2.C:CH.CH_2OH$
    $\overset{|}{CH_3}$
    Geraniol
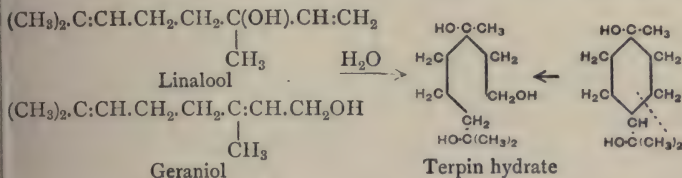
Terpin hydrate

By the action of dilute sulphuric acid on terpin hydrate numerous decomposition products are obtained, such as terpineol, cineol, terpinene, terpinolene, etc. Cineol is a constituent of many essential oils, and is to be considered as an inner anhydride of terpin,
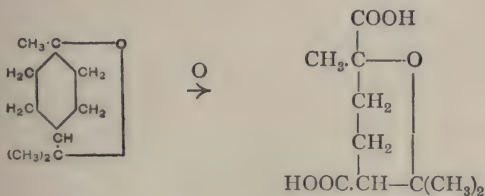
since its oxygen atom does not seem to possess either alcoholic, ketonic, aldehydic, or acidic properties. Potassium permanganate oxidizes it to the dibasic cineolic acid, which on dry distillation

decomposes into carbon monoxide and dioxide and methyl heptenone $(CH_3)_2C{:}CH.CH_2.CH_2.CO.CH_3$.

The oxidation products obtained from terpin vary with the oxidant used; thus nitric acid gives terebic acid, $C_7H_{10}O_4$, chromic acid gives a keto-lactone, $C_{10}H_{16}O_3$, which oxidizes further to acetic acid and terpenylic acid, $C_8H_{12}O_4$ (see dipentene, p. 61), whilst potassium permanganate gives acetic and oxalic acids.

Under the name of *terpineol* various products have been described which are now known to consist of mixtures of isomeric alcohols. Restricting the term to the tertiary alcohols, three isomers are known, α-terpineol (Δ.1-menthenol-8) m.p.35°; β-terpineol (Δ8(9)-menthenol-1) m.p. 32°, and γ-terpineol (Δ_4(8)-menthenol-1) m.p. 69° C. The ordinary (α) terpineol is prepared synthetically from pentane-$\alpha\gamma\epsilon$-tricarboxylic acid (see p. 53), this series of reactions giving rise to the inactive form, a similar result arising from the action of formic acid on geraniol. The active *d*-terpineol was obtained by Semmler from limonene hydrochloride by replacement of the halogen by the hydroxyl group. The constitution of terpineol follows from its synthesis as mentioned above. Since it is an unsaturated compound it readily forms a nitrosochloride, from which by elimination of hydrochloric acid a hydroxy-oxime is obtained, and this oxime on hydrolysis is converted into *i*-carvone, a series of reactions determining the structure of the latter ketone.
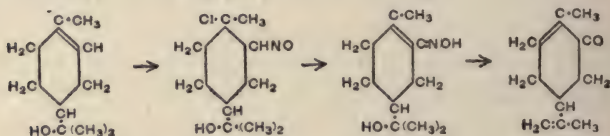
The β-terpineol is obtained by the fractionation of commercial terpineol, of which it constitutes the portion boiling between 212 and 215° C. Its constitution as a Δ8(9) derivative is shown by the fact that on oxidation with potassium permanganate it is converted into menthane-triol-1.8.9 (as was shown by Stephan and Helle), and the latter alcohol on further oxidation with chromic acid yields *p*-methyltetrahydroacetophenone and *p*-methyl-*p*-hydroxy-

hexahydroacetophenone, which can be still further oxidized to tetrahydro-*p*-toluic acid and to *p*-toluic acid respectively.
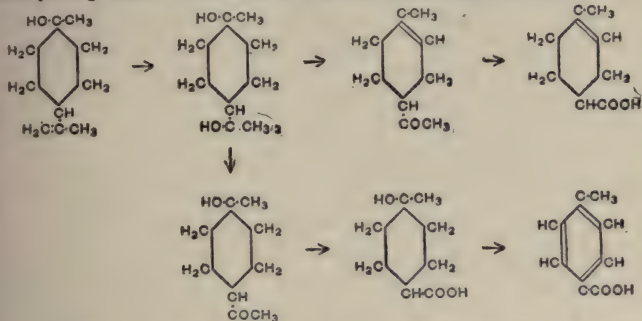
The γ-terpineol was obtained by Baeyer from dipentene dihydrobromide by converting the latter into 1.4.8-tribromomenthane, and reducing the latter with zinc dust and acetic acid to acetyl-Δ4(8)menthenol-1, which on hydrolysis with alcoholic potash yields the required terpineol (see p. 58). This terpineol on oxidation with potassium permanganate is converted into menthane tri-ol-1.4.8. Its constitution follows from the fact that it furnishes dipentene dihydrobromide by the action of hydrobromic acid dissolved in glacial acetic acid.

Wallach, in examining the Ceylon oil of cardamoms, isolated a terpineol different from the known forms. This terpineol has also been found in oil of marjoram, and is identical with the one formed by the action of aqueous alkali on terpinene dihydrochloride, or when sabinene is shaken with sulphuric acid. To distinguish it from the other terpineols, and to indicate its relationship to terpinene, it is called *terpinenol*. It is represented by the structural formula—
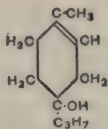
which readily accounts for its transformation into terpinene dihydrochloride by the action of hydrochloric acid, and for the

formation of the terpin of terpinene (m.p. $137°$ C.) by the action of dilute sulphuric acid—
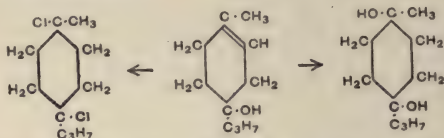
Terpinene dihydrochloride   Terpinenol   Terpin of terpinenol

On oxidation with potassium permanganate it yields a trihydroxy-1.2.4-menthane (which, when heated with acid, is transformed into carvenone and cymene), a more drastic oxidation of the latter leading to the formation of $\alpha\alpha^1$-dihydroxy-α-methyl-α^1-isopropyl adipic acid by the disruption of the ring between the second and third carbon atoms. This acid exists in two forms, one active and one inactive, and on further oxidation with acid potassium permanganate, yields a diketone which has been recognized as ω-dimethylacetonylacetone. This series of reactions may be thus illustrated—
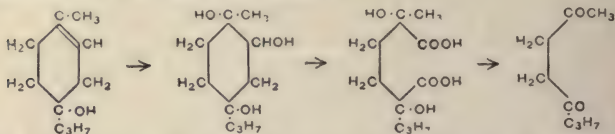
The inactive form of the above dibasic acid has been synthesized from dimethylacetonylacetone by condensing it with hydrocyanic acid, and hydrolyzing the nitrile thus obtained.

By the fraction of ordinary commercial terpineol, an isomeric terpinenol is obtained which has the structure of a $\Delta.3$-terpinenol, since on oxidation with potassium permanganate it yields a trihydroxy-1.3.4-menthane, capable of further oxidation to the same substituted adipic acid as the above terpinenol, but if heated with mineral acid does not yield carvenone but $\Delta.1$-menthenone-3.
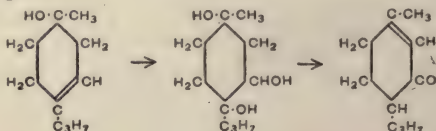
Confirmation of the above structure is given by the fact that this terpinenol may be obtained synthetically from the action of magnesium methyl iodide on Δ.3-isopropylcyclohexenone.

Among the ketones of this group, menthone, pulegone, and carvone are the most important. Ordinary menthone (p-menthanone-3), $C_{10}H_{18}O$, is found in oil of peppermint, and is prepared artificially by the oxidation of menthol with chromic acid. If this oxidation be carried out at 135° C. a d-menthone is obtained. The l-form is best obtained, according to Beckmann, by the oxidation of l-menthol, if the action of excess of acid be avoided as much as possible, as menthone is readily inverted by acid. This inversion gives rise to what Beckmann describes as d-menthone, but which should in all probability be described as d-isomenthone, since it does not seem to be a chemical individual but a mixture of l-menthone, and the, as yet, unisolated d-isomenthone. The reduction of pulegone hydrobromide also gives rise to menthone, but this menthone was shown by Martine to be not quite identical with ordinary l-menthone, and is designated by him as P-menthone. Several syntheses of menthone have been performed, the simplest being that of Barbier and Bouveault, by the action of acetic anhydride on l-rhodinal oxime (see p. 46). Einhorn and Klages have prepared an inactive menthone from β-methyl pimelic ester, which is transformed by the action of sodium ethoxide into methyl-1-cyclohexanone-3-carboxylic ester-4, the isopropyl group then being introduced into position 4 by the action of isopropyl iodide and sodium ethoxide. The resulting ester is then hydrolyzed and carbon dioxide eliminated from the carboxyl group, when i-menthone is produced.
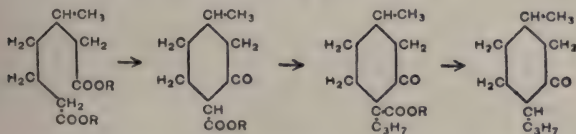
Haller and Martine have synthesized active menthone by the action of isopropyl iodide on the sodium derivative of methyl-1-cyclo-hexanone-3 (the sodium derivative of the ketone being

obtained by the use of sodamide), whilst Koetz and Hesse by condensation of the same ketone with ethyl oxalate and subsequent hydrolysis obtain methyl cyclohexanone carboxylic acid, the isopropyl derivative of which on heating with potassium hydroxide dissolved in methyl alcohol yields *d*-menthone.
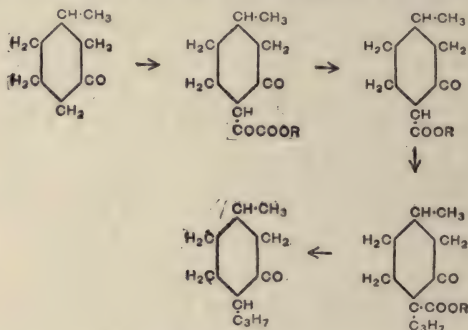
The constitution of this ketone follows from the various syntheses given above, and from the consideration of the various products which it yields on oxidation and decomposition with various reagents. The fact that phosphorus pentachloride converts it into a compound which by successive treatment with bromine and quinoline yields *m*-chlorocymene, indicates the presence of a six-membered ring with the methyl and isopropyl groups in the para position to each other; and since oxidation with potassium permanganate yields oxymenthylic acid, $C_{10}H_{18}O_3$, and finally β-methyl adipic acid, $C_7H_{12}O_4$, the existence of the reduced benzene ring with the keto group in the ortho position to the isopropyl group may be considered as definitely established.

Chlorocymene   Menthone   Oxymenthylic β-methyl adipic
                                   acid   acid
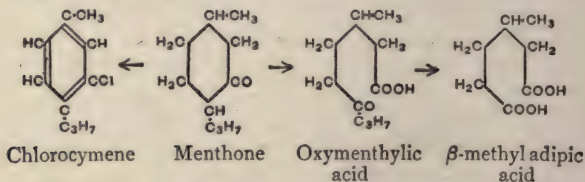
Menthone shows most of the characteristic properties of ketones,

but does not combine with acid sodium sulphite. As already mentioned under *Polymethylenes*, the oxime is converted by the action of phosphorus pentoxide into an iso-oxime. This iso-oxime, in the case of menthone, is converted on hydrolysis into the ε-amino-decylic acid.

$$
\begin{array}{ccccc}
\text{C}_3\text{H}_7.\text{CH}\,.\,\text{C:NOH} & & \text{C}_3\text{H}_7\text{CH}.\text{NH}.\text{CO} & & \text{C}_3\text{H}_7\text{CHNH}_2 \quad \text{COOH} \\
\mid \qquad \mid & & \mid \qquad \mid & & \mid \qquad\qquad \mid \\
\text{CH}_2\,\text{CH}_2 & \rightarrow & \text{CH}_2 \quad\; \text{CH}_2 & \rightarrow & \text{CH}_2 \qquad\; \text{CH}_2 \\
\mid \qquad \mid & & \mid \qquad \mid & & \mid \qquad\qquad \mid \\
\text{CH}_2.\text{CH}.\text{CH}_3 & & \text{CH}_2\!-\!\!-\!\text{CH}.\text{CH}_3 & & \text{CH}_2\!-\!\!-\!\text{CH}.\text{CH}_3
\end{array}
$$
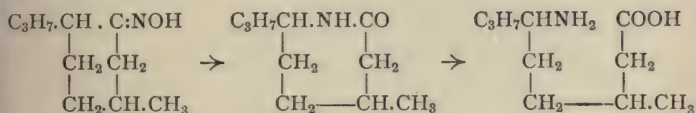
Pulegone ($\Delta.4(8)$-menthenone-3) is an unsaturated ketone found in oil of pennyroyal. It is a dextro-rotatory liquid boiling at 221° C. The synthesis of pulegone from citronellal has already been mentioned (p. 55), and the fact that the carbonyl group is in position 3 is shown by the conversion of pulegone into menthone. In the above-mentioned synthesis the formation of pulegone is brought about by the rearrangement of isopulegone under the influence of baryta water, and Harries and Roeder have shown that pulegone can be reconverted into isopulegone by heating pulegone hydrobromide with basic lead nitrate, the resulting isopulegone being a laevo-rotatory liquid.

Pulegone   Isopulegone
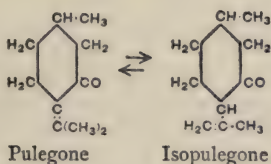
This reaction shows that the two ketones differ only in the position of the double bond, and possess consequently the same skeletal structure. This result is confirmed by the fact that pulegone on treatment with hydroxylamine yields an oxamino-ketone, a reaction characteristic of unsaturated ketones containing the group $>$C:C-CO, whilst in isopulegone the double bond would be in the $\beta\gamma$ position, and would pass into the $\alpha\beta$

position under the influence of alkalies, which is in accordance with the formation of a true oxime from isopulegone. A pulegone dioxime has also been obtained, the two compounds produced by the action of hydroxylamine under different conditions being represented as—

Pulegone hydroxylamine   Pulegone dioxime
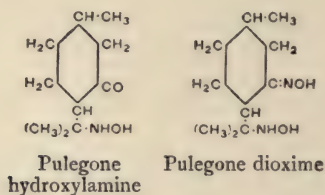
The position of the double bond in the 4(8) position is shown by the fact that pulegone on oxidation with potassium permanganate yields acetone and β-methyl adipic acid, confirmation of which is given by Wallach's observation that hydrolysis of pulegone by water at 250° C. leads to the formation of acetone and methyl-1-cyclohexanone-3.
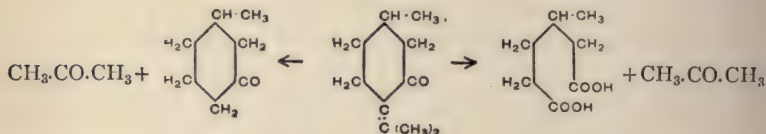
Carvone (Δ6.8(9) menthadiene-one-2), $C_{10}H_{14}O$, is found widely distributed in nature. The *d*-form is the chief constituent of oil of caraway, and the *l*-form is found in oil of spearmint. Synthetically it may be prepared from limonene by the action of alcoholic potash on the nitroso-chloride of this hydrocarbon, *l*-carvoxime being obtained. Hydrolysis of this oxime with sulphuric acid yields *l*-carvone. Similarly, terpineol nitroso-chloride, in the presence of sodium ethoxide, is converted into hydroxymenthenone-oxime, the hydrolysis of which by acids yields *i*-carvone. Thus this latter method leads to a complete synthesis of carvone since that of terpineol has been effected.

Limonene nitrosochloride   Carvone
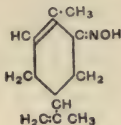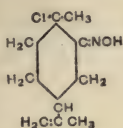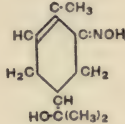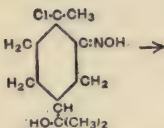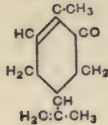
Terpineol nitrosochloride

Carvone does not yield a normal condensation product with acid sodium sulphite, but when boiled with this reagent is converted into sodium carvonedihydrodisulphonate, $C_{10}H_{16}O(NaSO_3)_2$, which is unaffected by alkali. The oxime, on treatment with concentrated sulphuric acid, passes into (p)aminothymol, cymylhydroxylamine probably being formed as an intermediate stage in the transformation—
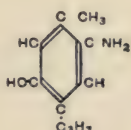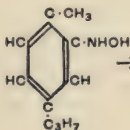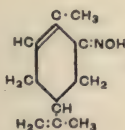
whilst if alcoholic sulphuric acid be used carvacrylamine is formed. When shaken with air in the presence of baryta, carvone undergoes autoxidation, barium peroxide being formed, together with methyl-1-propenyl-4-dihydroresorcin, identical with the ketone obtained (in the form of its dioxime) by the oxidation of oxaminocarvoxime—

Oxamino-carvoxime

Keto-form

Carvone

Enol-form
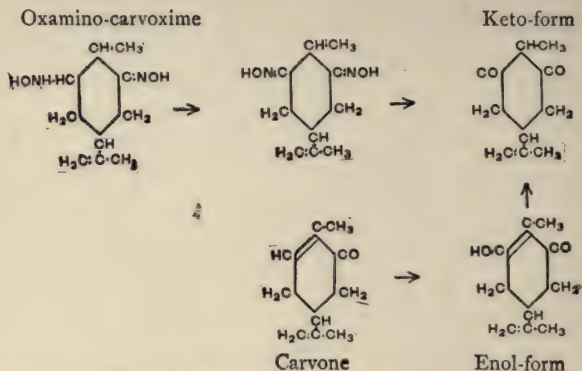
The constitution of carvone is determined by its synthesis from terpineol, and from its relationship to dihydrocarvone and dihydrocarveol into which it passes on reduction. This reaction determines the situation of one double bond in the 8(9) position, since the oxidation of dihydrocarveol leads to a menthane-triol-2.8.9, capable, as Tiemann showed, of further oxidation by chromic acid to a ketone alcohol, from which, by the action of sodium hypobromite, a hydroxy-acid was obtained. This acid must be a methyl cyclohexanol-carboxylic acid, since on heating with bromine to 190° C. it is converted into m-hydroxy-p-toluic acid.
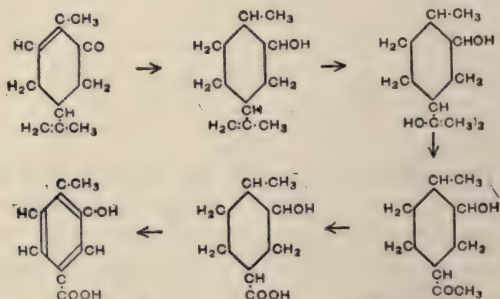
The position of the second double bond is shown by the oxidation of carvone by potassium permanganate to oxyterpenylic acid, and by the reduction of its hydrobromide to carvotan-

acetone. The latter, on oxidation with potassium permanganate, yields pyruvic acid and isopropyl succinic acid, a series of reactions showing that the double bond must be at position 6 in the nucleus.

Oxyterpenylic acid
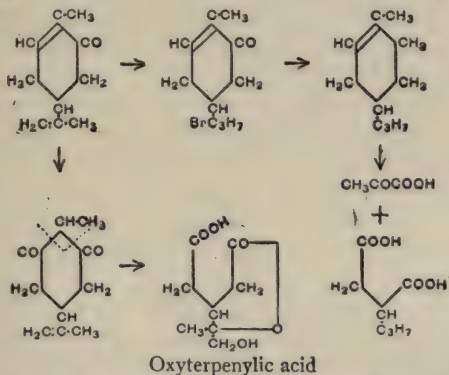
Bi-Cyclic Terpenes.—The members of this group contain two carbocyclic rings united with each other by two or three carbon atoms in common. A convenient system of nomenclature for the members of this group is due to Baeyer, who observed that each saturated hydrocarbon of the group contains two tertiary carbon atoms which are combined with each other three times, either directly or by means of intervening carbon atoms, the whole system forming a series of "bridges." To distinguish the bridges, the symbol o is used to describe the direct union of the tertiary carbon atoms, and the numerals 1, 2, 3, etc., to describe the number of carbon atoms that are present in the bridges between the tertiary carbon atoms. The hydrocarbons of the series, containing five carbon atoms, are described as bi-cyclo-pentanes, those with six carbon atoms as bi-cyclo-hexanes, and so on. Thus hydrocarbons of the following structure—
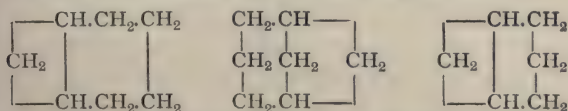
would be described as bi-cyclo (o.1.4) heptane, bi-cyclo (1.1.3)

heptane, and bi-cyclo (0.1.3) hexane, indicating, for example, in the first case that the tertiary carbon atoms were directly united, and also that they were united by two other bridges, containing respectively one and four carbon atoms.

In the bi-cyclo (0.1.3) hexane series the most important compounds are the hydrocarbon thujene, $C_{10}H_{16}$, and its derivatives, and the isomeric sabinene, $C_{10}H_{16}$, and its derivatives. The chief naturally occurring compound of the series is the ketone *thujone* (tanacetone), $C_{10}H_{16}O$, which is found in many essential oils. It has been questioned for some time whether the thujones obtained from different sources were identical or not, and Wallach has shown that even if they be considered as identical chemical individuals, they differ markedly in their physical aspects. He concludes that certainly two, if not three forms exist ; thus oil of thuja contains chiefly α-thujone, which is a lævorotatory liquid, boiling at 200°-210° C., and forming two semicarbazones, melting respectively at 187° C. and 110° C., whilst oil of absinthe contains principally β-thujone, which is dextro-rotatory, and yields a semicarbazone, which is dimorphous, and melts at 175° C. or 170-172° C. The isomeric thujones may be separated by the fractional crystallization of their semicarbazones from methyl alcohol. When warmed with alcoholic potash, the β-variety is partially converted into the α-form. Thujone shows the usual properties of a ketone, it combines with sodium bisulphite and forms semicarbazones and oximes. The α-form on reduction gives thujyl alcohol, $C_{10}H_{17}OH$, which, on re-oxidation, yields β-thujone. Both varieties of the ketone, when oxidized with cold potassium permanganate, yield the isomeric monobasic ketonic acids, $C_{10}H_{16}O_3$, known as thujaketonic acids (α and β). The constitution of thujone has been determined by Semmler from a study of its oxidation products. The thuja-ketonic acids contain the grouping – $CO.CH_3$, since in the presence of bromine and an alkaline hydroxide they are further converted into two dibasic acids of composition $C_9H_{14}O_4$, with simultaneous formation of bromoform. α-Thujaketonic acid is a saturated acid, and on heating to 150° C. passes into the β-acid, which is unsaturated, so that the former probably contains a cyclic complex,

whilst in its transformation to the β-form, ring fission occurs, and the β-acid results as an open chain compound. The acids $C_9H_{14}O_4$ were called respectively α and β-tanacetogen dicarboxylic acids, and the β-acid, on oxidation with potassium permanganate, is transformed into ω (or δ)-dimethyl laevulinic acid $(CH_3)_2.CH.CO.CH_2.CH_2COOH$, which had been earlier obtained by Fittig from $\beta\gamma$-dibromo-isoheptane acid, and also by Conrad from the ester $(CH_3O_2C)_2CH.CH_2.CO.C(CH_3)_2.CO_2CH_3$ (formed by the action of γ-bromodimethyl aceto-acetic acid dimethyl ester and sodio-malonic acid methyl ester), by heating it with sulphuric acid. Again, β-thujaketonic acid, on oxidation by potassium permanganate, yields a diketone, $C_8H_{14}O_2$, and this, when heated with alcoholic ammonia, passes into α-methyl-α^1-isopropyl pyrrol, a reaction showing the presence of the isopropyl group in the diketone, and also that it is a γ-diketone, since only such diketones yield pyrrol derivatives. Thus the diketone seems to be ω-dimethyl acetonyl-acetone $(CH_3)_2CH.CO.CH_2.CH_2.CO.CH_3$, and it would appear most probable, from these reactions, to regard β-tanacetogen dicarboxylic and β-thujaketonic acids as—

$$\begin{array}{cc}
\overset{\displaystyle CH\text{---}COOH}{\underset{\displaystyle (CH_3)_2.CH.\overset{\|}{C}.CH_2.CH_2.COOH}{}} & \overset{\displaystyle CH.COOH}{\underset{\displaystyle (CH_3)_2.CH.\overset{\|}{C}.CH_2.CH_2.CO.CH_3}{}}
\end{array}$$
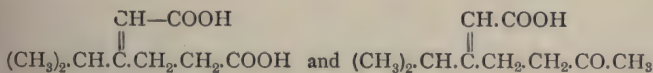
whilst the corresponding α-acids may be looked upon as possessed of the following structures :—

$$\begin{array}{cc}
\begin{array}{l}
\text{---- CH.COOH} \\
\text{CH}_2\text{--- C.CH(CH}_3)_2 \\
\text{CH}_2.\text{COOH}
\end{array} &
\begin{array}{l}
\text{CH}_2.\text{COOH} \\
\text{CH}_2\text{--- C.CH(CH}_3)_2 \\
\text{---- CHCOCH}_3
\end{array}
\end{array}$$

and thujone itself as—

$$\begin{array}{c}
CH(CH_3)_2 \\
\text{---- C --- CH}_2 \\
CH_2 \quad\quad CO \\
\text{---- CH --- CH.CH}_3
\end{array}$$
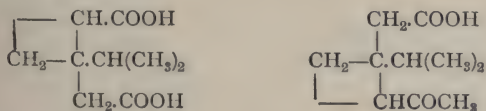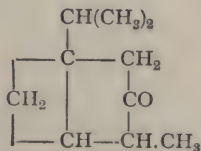
Thujone is converted into carvacrol when boiled with ferric chloride, and when heated alone to 280° C., passes into the isomeric carvotanacetone, a Δ.6-menthenone-2, since this ketone on reduction passes into tetrahydrocarvone, and also on oxidation yields pyruvic acid and isopropylsuccinic acid (p. 77). When heated with dilute sulphuric acid, thujone is transformed into isothujone, a ketone of the cyclopentane series, formed by the fission of the cyclopropane ring of the original thujone. The constitution of this isothujone was determined by Semmler, who found that on oxidation with potassium permanganate it yielded a keto-lactone, $C_{10}H_{16}O_3$, from which, by further oxidation, a ketonic acid, $C_8H_{14}O_3$, is produced. This acid is β-isopropyl-laevulinic acid, since on further oxidation by bromine in alkaline solution it gives isopropyl succinic acid.

$$
\begin{array}{ccccc}
\text{CH(CH}_3)_2 & & \text{CH(CH}_3)_2 & & \text{CH(CH}_3)_2 \\
| & & | & & | \\
\text{—C——CH}_2 & & \text{CH—CH}_2 & & \text{CH —— CH}_2 \\
| \quad | & \rightarrow & | \quad | & \longrightarrow & | \quad | \\
\text{H}_2\text{C} \quad \text{CO} & & \text{CO} & & \text{CO} \\
| \quad | & & | & & | \\
\text{—CH—CH.CH}_3 & & \text{CH}_3.\text{C = C.CH}_3 & & \text{CH}_3.\text{CO.C(CH}_3)\text{—O} \\
\text{Thujone} & & \text{Isothujone} & & \downarrow
\end{array}
$$

$$
\begin{array}{ccc}
\text{HOOC.CH.CH(CH}_3)_2 & \longleftarrow & \text{CH}_3\text{CO.CH.CH(CH}_3)_2 \\
| & & | \\
\text{CH}_2.\text{COOH} & & \text{CH}_2.\text{COOH}
\end{array}
$$
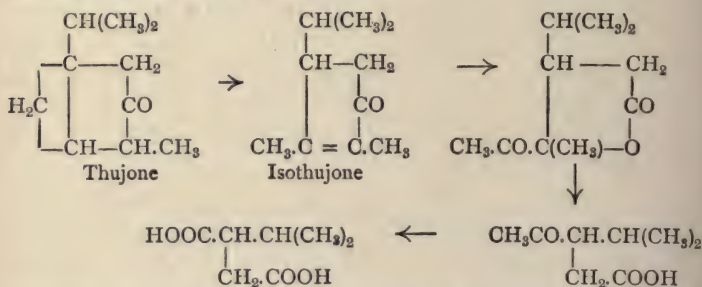
The above reactions are thus explained on the assumption of isothujone as a cyclopentene-one, and also favour the configuration of thujone as a bi-cyclo compound. As an alternative to the above formula of isothujone, one might be given in which the positions of the $>CH.CH(CH_3)_2$ and the $>CH_2$ groups were interchanged, leading to the formation of a keto-lactone and of α-isopropyl-laevulinic acid on oxidation, but this structure is negatived by the fact that isothujone gives rise to a benzylidene derivative when acted upon by benzaldehyde in the presence of sodium ethoxide, a fact necessitating the presence of the $-CH_2.CO-$ grouping.

The reduction of thujone oxime leads to the formation of thujylamine, $C_{10}H_{17}NH_2$; and Semmler, by distillation of the hydro-

chloride of this base, obtained a hydrocarbon $C_{10}H_{16}$, which he called *thujene*. Somewhat later, however, Tschugaeff, by the distillation of the methyl xanthogenate of thujyl alcohol, obtained a hydrocarbon differing from that of Semmler, the hydrocarbon of the latter investigator apparently being a monocyclic compound, and containing two double bonds. Consequently, Tschugaeff considers that it is derived from isothujone by the group $- CH_2 - CO -$ becoming $- CH = CH -$, and so designates it as isothujene. The thujene obtained by the xanthogenic reaction is called α-thujene to distinguish it from the isomeric β-thujene obtained by the distillation of trimethyl-thujyl ammonium hydroxide, the two hydrocarbons differing merely in the position of the double bond.
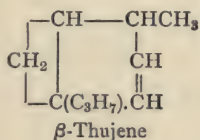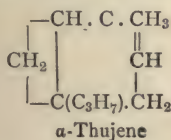
α-Thujene does not form either a crystalline nitrosochloride or a crystalline bromo-additive compound. It instantaneously decolourizes potassium permanganate solution, and rapidly resinifies on exposure. Its molecular refraction is 44.21, the calculated value for a bi-cyclic terpene being 43.54. β-thujene differs from the α-form by its much greater rotatory power, and it seems probable that thujone on reduction to thujyl alcohol yields two stereo-isomeric thujyl alcohols, the elimination of water from which can take place in two directions, giving rise to the two different hydrocarbons, since β-thujene is obtained by the xanthogenic process also.

Sabinene, $C_{10}H_{16}$, is a hydrocarbon obtained from oil of savine by fractional distillation. It is a dextro-rotatory liquid of molecular refraction 44.9, the calculated value derived from its refractive index (1.466) for a bi-cyclic hydrocarbon with one double bond being 44.4. On oxidation with potassium permanganate it yields sabinene glycol $C_{10}H_{18}O_2$, and a hydroxy-acid sabinenic acid $C_{10}H_{16}O_3$, whilst if lead peroxide be used as oxidant,

sabinene ketone $C_9H_{14}O$ is formed. Sabinene ketone when boiled with dilute acids is converted into dihydro-cuminic alcohol, which on oxidation with chromic acid yields cuminic alcohol (p-isopropyl benzyl alcohol) $C_3H_7.C_6H_4.CH_2OH$; whilst sabinenic acid on distillation in vacuo passes into cuminic acid (p-isopropyl benzoic acid) $C_3H_7.C_6H_4.COOH$. The constitution of sabinene is partially derived from that of *sabinol* $C_{10}H_{15}OH$, an unsaturated alcohol which constitutes the chief portion of oil of savine. This alcohol on oxidation with a dilute solution of potassium permanganate is converted into sabinol glycerine $C_{10}H_{15}(OH)_3$, a reaction indicating the presence of the $-C=C-$ grouping, the glycerine passing into cuminic alcohol $C_3H_7(1).C_6H_4.CH_2OH(4)$ in the presence of traces of mineral acid. Again, by further oxidation, sabinol glycerine yields α-tanacetone dicarboxylic acid, a reaction pointing to the double bond in sabinol being outside the ring system, as otherwise the formation of the group $-CH_2OH$ in the cuminic derivatives would be impossible. Thus the above compounds may be formulated—

Sabinol   Sabinol glycerine α-Tanacetone dicarboxylic acid

Sabinene   Sabinene glycol   Sabinenic acid
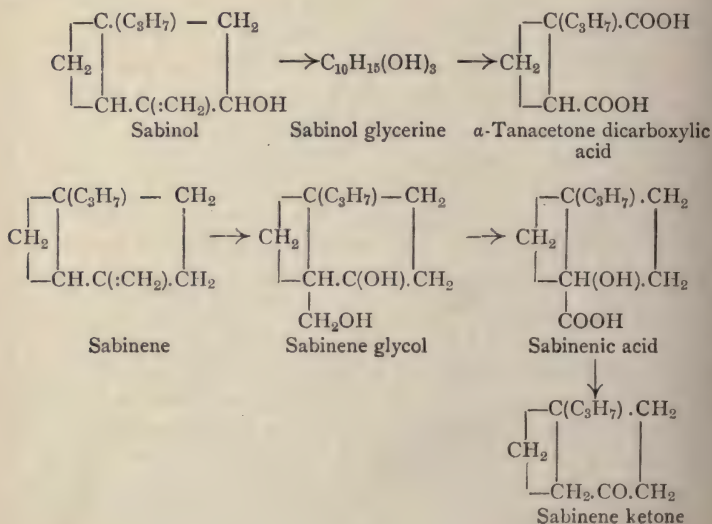
Sabinene ketone

A certain amount of confirmation of the above formulæ is given by the observations of Wallach that sabinene ketone is converted into isopropyl-1-cyclohexene-2-one-4 by the action of mineral acids, and that this ketone, on treatment with the Grignard re-agent, passes into α-phellandrene, of which the structure is known.

$$\begin{array}{c}\underset{\displaystyle\rule{0pt}{2em}}{CH_2}\left|\begin{array}{c}---CH.CO.CH_2\\[1em]---C(C_3H_7).CH_2\end{array}\right.\end{array}\quad\longrightarrow\quad\begin{array}{c}CH_2.CO.CH_2\\[1.5em]CH:C.CH_2\\CH(CH_3)_2\end{array}\quad\longrightarrow\quad\begin{array}{c}CH.CO.CH_2\\[1em]CH.CH.CH_2\\CH(CH_3)_2\\\downarrow\\CH.C(CH_3){:}CH\\[1.5em]CH.CH.CH_2\\CH(CH_3)_2\end{array}$$

Sabinene ketone   α-Phellandrene
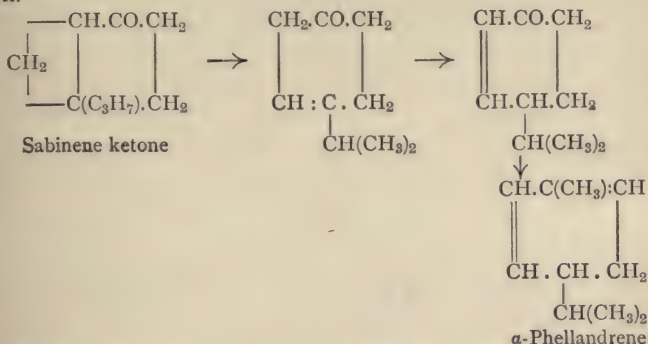
The more important bi-cyclo-terpenes and their derivatives are those of the bi-cyclo (1.1.3)-heptane group, comprising as its chief member pinene, and those of the corresponding (1.2.2) group, which includes as its more important derivatives bornylene, camphene, and fenchene, and the corresponding alcohol and ketone derivatives.

Pinene, $C_{10}H_{16}$, is the chief constituent of oil of turpentine, the *l*-form being found in the French oils, whilst the *d*-form is found in the Swedish, Russian, and American oils of turpentine. It absorbs oxygen from the air, with formation of resinous products. When heated with iodine it yields cymene. Dilute nitric acid oxidizes it to terephthalic acid and other acids, chiefly of the aliphatic series. It behaves as an unsaturated compound, forming a nitrosochloride and a dibromide. Its hydrochloride is a colourless solid known as "artificial camphor." This hydrochloride is identical with bornyl chloride, and on removal of hydrogen chloride by a weak alkali, passes into camphene. Nitric acid in aqueous alcohol solution converts pinene into terpin hydrate whilst in the presence of organic acids it is converted into ester,

of terpineol. The determination of the constitution of pinene
has been a long and complicated process, the earlier experimental
work being in the main incorrect, and it is chiefly to the investi-
gations of Wagner and of Baeyer at the end of the last century
that we owe our present knowledge of the structure of this hydro-
carbon. The chief decompositions of pinene, together with its
products of oxidation, are shown in the following chart :—

Dipentene

Pinene Nitrosochloride   *p*-Cymene

                                              Heat and Iodine

Terpineol   ←——   PINENE   ——→   Terpinene
             acid

                                              Terpenylic acid }
                         moist air   Acetic acid
        acid]   and
        oxidants   sunlight   O

{ Terephthalic acid   Sobrerol → Pinol   →O   Pinol glycol
  Terebic acid

Pinene glycol   α-Pinonic acid   Pinoyl-formic acid   Nopic acid

Homoterpenylic }   Pinic acid   Homoterpenoyl-   Nopinone
methyl ketone   formic acid

                    Norpinic acid   Homo-
                                                          terpenylic acid
                    Keto-isocamphor-
Dimethyl-   onic acid
tricarballylic   Isoketocamphoric acid }
acid   Isocamphoronic acid }   Terpenylic acid

                                            Terebic acid

The constitution of pinene is derived in the following manner.
The oxidation of the hydrocarbon with one per cent. potassium
permanganate yields pinene glycol $C_{10}H_{16}(OH)_2$, which, on
treatment with very dilute hydrochloric acid, passes into pinol
$C_{10}H_{16}O$, and this latter compound, on oxidation with more

potassium permanganate, is converted into terpenylic acid. Since terpenylic acid possesses the structure [1]

$$\begin{array}{ccc} CH_2\!\!-\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!-\!\!-\!\!CH_2 \\ | & | & | \\ COOH & C(CH_3)_2 & | \\ & | & \\ & O\!\!-\!\!-\!\!-\!\!CO \end{array}$$
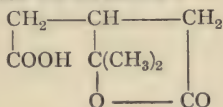
it follows that pinol contains the skeleton system

$$\begin{array}{ccc} CH_2\!\!-\!\!CH\!\!-\!\!-\!\!CH_2 \\ | & | & | \\ C: & C(CH_3) & \\ & | & \\ & O\!\!-\!\!-\!\!C: \end{array}$$
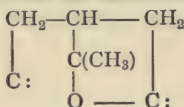
to which must be now attached a hydrogen atom and the group $(CH_3.C)$, the latter group being necessary to account for the transformation of the pinene molecule into paracymene derivatives. The addition may take place in two ways, giving rise to compounds of structure

$$I \quad \begin{array}{c} CH_2\!\!-\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!-\!\!| \\ | \quad C(CH_3)_2 \quad | \\ | \quad | \quad CH_2 \\ | \quad O \\ CH:C(CH_3).CH\!\!-\!\!-\!\!-\!\!| \end{array} \quad or \quad \begin{array}{c} CH_2\!\!-\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!| \\ | \quad C(CH_3)_2 \quad | \\ | \quad | \quad CH_2 \quad II \\ | \quad O \\ CH_2.C(CH_3):C\!\!-\!\!-\!\!-\!\!| \end{array}$$
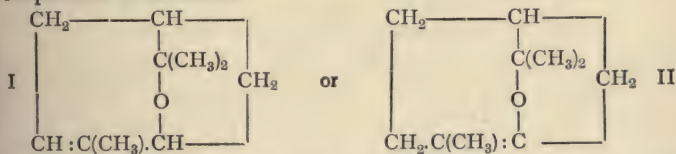
and since pinol, by the addition of a molecule of water (a reaction carried out by the decomposition of its hydrobromic acid addition compound with sodium hydroxide), passes into sobrerol (pinol hydrate), the latter must be either

$$I(a) \quad \begin{array}{c} CH_2\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!-\!\!-\!\!CH_2 \\ | \quad C(CH_3)_2.OH \quad | \\ | \quad | \\ CH=C(CH_3)\!\!-\!\!-\!\!-\!\!-\!\!CHOH \end{array} \quad or \quad \begin{array}{c} CH_2\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!-\!\!CH_2 \\ | \quad C(CH_3)_2OH \quad | \\ | \quad | \\ CH_2\!\!-\!\!-\!\!C(CH_3)=C.OH \end{array} \quad II(a)$$

---
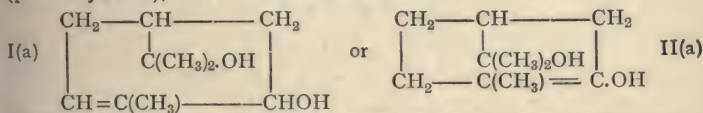
[1] This structural formula for the acid has now been definitely established by the synthesis of the acid by Simonsen from ethyl β-acetyl glutarate and magnesium methyl iodide, the resulting lactonic ester, on hydrolysis with hydrochloric acid, yielding terpenylic acid.

$$ROOC.CH_2.CH(COCH_3).CH_2.COOR \xrightarrow{MgCH_3I} \\ ROOC.CH_2.CH[C(CH_3)_2.OMgI].CH_2.COOR$$

$$\begin{array}{c} (CH_3)_2C\!\!-\!\!-\!\!-\!\!-\!\!CH.CH_2.COOH \\ | \quad | \\ O\!\!-\!\!CO\!\!-\!\!CH_2 \end{array} \leftarrow \begin{array}{c} (CH_3)_2C\!\!-\!\!-\!\!-\!\!-\!\!CH.CH.COOR \\ | \quad | \\ O\!\!-\!\!CO\!\!-\!\!CH_2 \end{array}$$
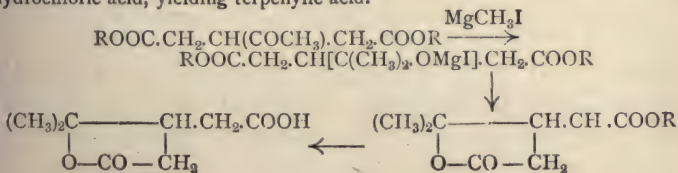
but now, as the oxidation of sobrerol leads to the production of sobrerythrite, which is a tetrahydric alcohol, it follows that sobrerol must be of the structure I(a), because a compound of structure II(a) would give rise to an oxy-ketone on oxidation. Consequently, pinol must be represented by formula I, which leads to the following representation of pinene :—

$$
\begin{array}{c}
\text{CH}_2\text{———CH———} \\
| \quad\quad\quad\quad\quad | \\
| \quad\quad \text{C(CH}_3)_2 \ \text{CH}_2 \\
| \quad\quad\quad | \\
\text{CH : C(CH}_3)\text{.CH———}
\end{array}
$$
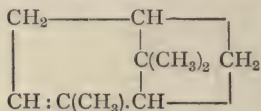
Confirmation of this is given by Baeyer's oxidation of pinene to α-pinonic acid, pinic acid, and other products (see Cap. I. p. 13).

A substance closely related to pinene is the ketone nopinone, a substance formed by the action of potassium permanganate and concentrated sulphuric acid on sodium nopate.

$$
\begin{array}{c}
\text{——CH}_2\text{——CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{CH}_2 \ \text{C(CH}_3)_2 \ \text{CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{——CH——C(OH)COOH}
\end{array}
\quad \xrightarrow{\text{O}} \quad
\begin{array}{c}
\text{——CH——CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{CH}_2 \ \text{C(CH}_3)_2 \ \text{CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{——CH——CO}
\end{array}
$$
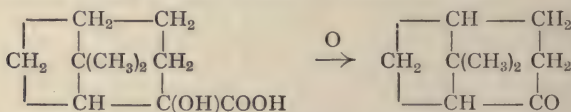
The ketone condenses readily with bromo-acetic ester in the presence of zinc to form nopinole acetic ester, from which the free nopinole acetic acid is obtained in small yields on hydrolysis. When this acid is heated with acetic anhydride it yields a mixture of two unsaturated acids, one of which is very unstable, and during the reaction loses carbon dioxide and passes into β-pinene (the semi-cyclic isomer of ordinary pinene).

$$
\begin{array}{c}
\text{——CH———CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{CH}_2 \ \text{C(CH}_3)_2 \ \text{CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{——CH———C(OH)CH}_2\text{COOH}
\end{array}
\quad \longrightarrow \quad
\begin{array}{c}
\text{——CH——CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{CH}_2 \ \text{C(CH}_3)_2 \ \text{CH}_2 \\
| \quad\quad | \quad\quad | \\
\text{——CH——C : CH}_2
\end{array}
$$
$$\text{Nopinole acetic acid} \quad\quad\quad\quad\quad\quad\quad\quad \beta\text{-pinene}$$
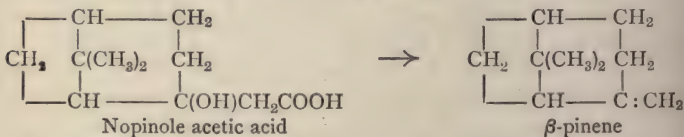
Camphene, $C_{10}H_{16}$, is found as a constituent of oil of citronella, oil of camphor, oil of rosemary, and also of French and American oils of turpentine. It may be obtained by heating pinene with sulphuric acid, but, according to Konowalow, is best prepared by

heating borneol with dilute sulphuric acid ($1 : 2$) for several hours at 60-100° C., with continual shaking. It is known in the d-, l-, and racemic forms. Numerous oxidation products are obtained from the hydrocarbon by the use of different oxidizing agents. Thus, with chromic acid it yields camphor; with chromyl chloride, camphenylanic aldehyde $C_{10}H_{16}O$; with dilute nitric acid, carboxyapocamphoric acid $C_7H_{11}(COOH)_3$; and with dilute potassium permanganate solution, camphenilone $C_9H_{14}O$, camphene glycol $C_{10}H_{16}(OH)_2$, camphenylic acid $C_{10}H_{16}O_3$, and camphene-camphoric acid $C_{10}H_{16}O_4$. A large number of investigations have been undertaken with the object of deciding the constitution of camphene, and the concensus of opinion is now in favour of the semi-cyclic structure of the hydrocarbon.

Confirmation of this structure has been sought by Semmler in the action of ozone on camphene, the ozonide obtained decomposing in two ways, either with the production of camphenilone and δ-oxycamphenilonic acid, or by loss of water into two acids $C_9H_{14}O_2$, of which the structure has not yet been determined. The former decomposition may be illustrated as follows :—

$$
\begin{array}{ccccc}
\mathrm{CH_2.CH.C\!:\!CH_2} & & \mathrm{CH_2.CH.C(O_3).CH_2} & & \mathrm{CH_2.CH.CO} \\
\mid\quad\;\;\mathrm{CH_2}\mid & \rightarrow & \mid\quad\;\;\mathrm{CH_2}\mid & \rightarrow & \mid\quad\;\;\mathrm{CH_2}\mid \\
\mathrm{CH_2.CH.C(CH_3)_2} & & \mathrm{CH_2.CH.C(CH_3)_2} & & \mathrm{CH_2.CH.C(CH_3)_2} \\
& & & & \text{Camphenilone} \\
\end{array}
$$

$$
+ \quad
\begin{array}{c}
\mathrm{CH_2.CH.COOH} \\
\mid\quad\;\;\mathrm{CH_2}\mid \\
\mathrm{CH_2.CH.C(CH_3)_2.OH}
\end{array}
$$
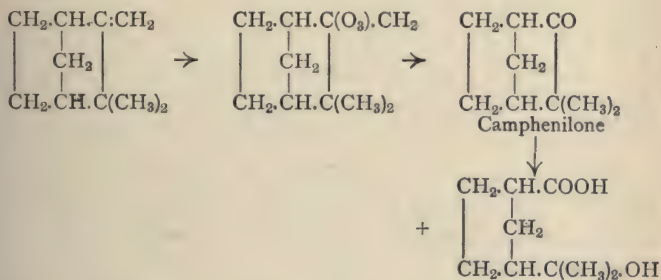
These reactions show that camphene could not possess an unsaturated nucleus, for if that were the case then the ozonide should yield a di-aldehyde on decomposition, and further, the splitting off of a carbon atom in the formation of the decomposition products of the ozonide confirms its semi-cyclic constitution. The various oxidation products of camphene can consequently be represented as

$$\begin{array}{ccc}
CH_2.CH.C(OH).CH_2OH & CH_2.CH.C(OH).COOH & CH_2.CH \!-\! CH_2 \\
\quad\mid\ \ CH_2\ \mid & \quad\mid\ \ CH_2\ \mid & \quad\mid\ \ C(CH_3)_2\ \mid \\
CH_2.CH.C(CH_3)_2 & CH_2.CH.C(CH_3)_2 & CH_2.C(CH_3).CO \\
\textbf{Camphene glycol} & \textbf{Camphenylic acid} & \textbf{Camphor}
\end{array}$$

$$\begin{array}{c}
\downarrow \\
CH_2.CH.CH_2.COOH \\
\mid\ \ C(CH_3)_2\ \mid \\
CH_2.CH.COOH \\
\textbf{Camphene-camphoric acid}
\end{array}$$
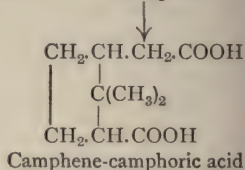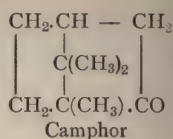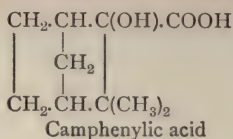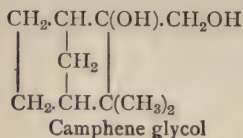
Still further confirmatory evidence is given by the fact that camphenilone when heated with sodamide yielded the amide of dihydrocampholenic acid, a compound synthesized by Bouveault from β-isopropyladipic anhydride in the following manner. The anhydride when heated yielded 3-isopropylcyclopentanone, which was then reduced to the corresponding alcohol. This alcohol was converted into its bromo-derivative, the ether solution of which on treatment with magnesium and carbon dioxide gave a carboxylic acid, the amide of this acid being identical with that of dihydrocampholenic acid.

$$\begin{array}{cccc}
CH_2\!-\!CH.C_3H_7 & CH_2.CH.C_3H_7 & CH_2.CH.C_3H_7 & CH_2.CH.C(CH_3)_2 \\
CH_2\ \ CH_2 & CH_2\ \ CH_2 & CH_2\ \ CH_2 & CH_2\ \ CH_2 \\
CO.O.CO & CO.CO & CH.CH.COOH & CH.CH\!-\!CO \\
 & & & \textbf{Camphenilone}
\end{array}$$
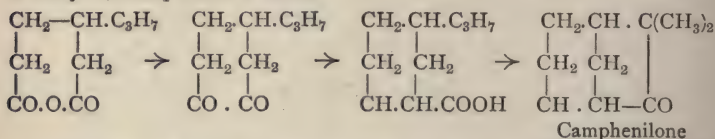
Fenchene, $C_{10}H_{16}$, is not found in any naturally occurring products, but may be prepared by the elimination of the elements of water from fenchyl alcohol, the reduction product of fenchone. Agreement has not yet been reached regarding the constitution of fenchone, and consequently that of fenchene cannot be settled, the only derivative of the series which may be considered as absolutely fixed being dihydrofencholenamide, the substance obtained by the inter-action of fenchone and sodamide. This substance has been synthesized by Bouveault and Levallois from dihydrocampholenic acid (see above). The acid was converted into its chloride, which by the Friedel and Crafts reaction was then transformed into its phenyl ketone. Sodamide reacts

with the ketone to yield a sodium derivative, in which the sodium atom is readily replaced by the methyl group, and the resulting ketone then undergoes the normal decomposition with sodamide, which leads to the formation of benzene and dihydrofencholenamide.

$$
\begin{array}{ccccc}
CH_2.CH.C_3H_7 & & CH_2.CH.C_3H_7 & & CH_2.CH.C_3H_7 \\
| \quad CH_2 & \rightarrow & | \quad CH_2 & \rightarrow & | \quad CH_3 \\
| & & | & & | \\
CH_2.CH.COOH & & CH_2.CH.COC_6H_5 & & CH_2.C(CH_3).COC_6H_5
\end{array}
$$

$$
\begin{array}{c}
\downarrow \\
CH_2.CH.C_3H_7 \\
| \quad CH_2 \\
| \\
CH_2.C(CH_3).CONH_2
\end{array}
$$
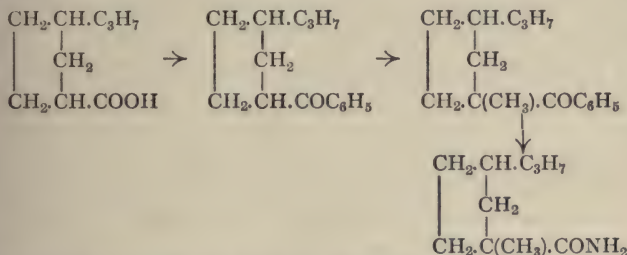
This reaction would seem to point to fenchone as most probably being possessed of the following structure :—

$$
\begin{array}{c}
CH_2.CH\!-\!\!-\!\!-C(CH_3)_2 \\
| \quad CH_2 \quad | \\
CH_2.C(CH_3).CO
\end{array}
$$
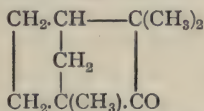
Of the ketones of the bi-cycloterpenes the most important is *camphor* $C_{10}H_{16}O$, the *d*-form of which is found in the camphor tree (*Laurus camphora*), whilst the *l*-variety occurs in the oil of *Matricaria parthenium*. The ordinary camphor of commerce is obtained, together with oil of camphor, by the distillation of the wood of the camphor tree with steam, and is finally purified by sublimation, generally with quicklime and charcoal. It crystallizes in prisms, and is readily soluble in the ordinary organic solvents. It sublimes readily, and boils at 209° C. The *d*-form has been obtained synthetically by Haller, by the distillation of calcium homocamphorate. A vast amount of experimental investigation has been carried out in order to settle the constitution of camphor, and the earlier experimenters were led to incorrect conclusions owing to the ease with which the ketone is transformed into benzenoid derivatives, such, for example, as the production of *p*-cymene and carvacrol when the ketone is heated with phosphorus pentoxide, of *m*-cymene and tetramethyl-

benzene when phosphorus pentasulphide is used, and of carvacrol, a-ethyl orthoxylene and a-tetramethylbenzene when camphor is heated with iodine, these results being explained in the light of modern knowledge by the occurrence of intra-molecular change in the molecule. Numerous oxidation products of camphor have been obtained by working under different conditions, thus with nitric acid it yields the dibasic camphoric acid $C_8H_{14}(COOH)_2$, camphoronic acid $C_6H_{11}(COOH)_3$ and other products; with potassium permanganate or chromic acid, camphoric acid is obtained, whilst if Caro's acid be used as oxidant campholid $C_{10}H_{16}O_2$ and a compound $C_{10}H_{16}O_4$ result.

The structural formula which at present is given to camphor rests on Bredt's investigations on camphoronic acid and also on the following facts. Camphor is a ketone since it yields an oxime, a hydrazone, and a semicarbazone, whilst on reduction it passes into a secondary alcohol (borneol) from which camphor can again be regenerated by ordinary oxidation processes. It is also a saturated ketone, and may consequently be regarded as containing two closed carbon rings attached to a $-CO$ group. The carbonyl group is attached to the $-CH_2-$ group since oxidation of camphor gives the saturated dicarboxylic camphoric acid $C_8H_{14}(COOH)_2$ which can only be explained on the assumption

$$C_8H_{14} \begin{array}{|c} \hline CH_2 \\ \\ CO \\ \hline \end{array} \quad \overset{O}{\rightarrow} \quad C_8H_{14}(COOH)_2$$
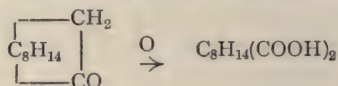
and further evidence of this structure is given by the fact that camphor combines with aldehydes in the presence of sodium ethoxide to form alkylidene compounds, and it also yields an isonitroso- and an oxymethylene derivative, reactions only shown by ketones containing the grouping $-CH_2.CO-$,

$$C_8H_{14} \begin{array}{|c} \hline C:NOH \\ \\ CO \\ \hline \end{array} \quad \text{and} \quad C_8H_{14} \begin{array}{|c} \hline C:CHOH \\ \\ CO \\ \hline \end{array}$$
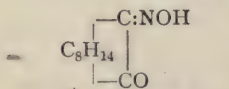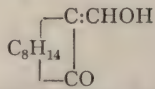
Isonitrosocamphor   Oxymethylene-camphor

As still further arguments in favour of this grouping may be mentioned the facts that it yields only mono- and disubstitution

derivatives, and that with aliphatic saturated ketones the position
of substitution is at the carbon atom adjacent to the – CO group.
Again, the α-bromo-camphor has been shown by Lowry to yield a
mixture of two stereoisomeric bromo-chloro-camphors on chlorin-
ation, and these are transformed into the same α-chlorocamphor
on treatment with alkali, consequently both halogen atoms must
be attached to the same carbon atom.

$$C_8H_{14}\begin{vmatrix}-CHBr\\[4pt]-CO\end{vmatrix} \rightarrow C_8H_{14}\begin{vmatrix}-CBr.Cl\\[4pt]-CO\end{vmatrix} \rightarrow C_8H_{14}\begin{vmatrix}-CHCl\\[4pt]-CO\end{vmatrix}$$
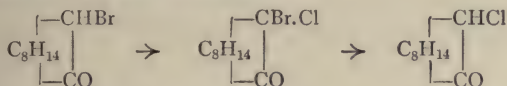
The relationship existing between camphor and camphoric
acid has also been shown in the following manner by Haller.
Camphoric anhydride on reduction by sodium amalgam yields
campholide, which, on treatment with potassium cyanide and sub-
sequent hydrolysis, passes into homocamphoric acid, from which
camphor may be regenerated by distillation of the barium or
calcium salt ; or cyanogen gas if brought into contact with freshly
prepared sodium camphor yields cyancamphor, which may be
directly hydrolyzed to homocamphoric acid.

$$C_8H_{14}(CO)_2O \rightarrow C_8H_{14}\begin{vmatrix}-CH_2\\[4pt]O\\[4pt]-CO\end{vmatrix} \rightarrow \underset{\begin{matrix}|\\COOK\end{matrix}}{\overset{\begin{matrix}CH_2CN\\|\end{matrix}}{C_8H_{14}}} \rightarrow \underset{\begin{matrix}|\\COOH\end{matrix}}{\overset{\begin{matrix}CH_2COOH\\|\end{matrix}}{C_8H_{14}}}$$

$$C_8H_{14}\begin{vmatrix}-CHNa\\[4pt]-CO\end{vmatrix} \rightarrow C_8H_{14}\begin{vmatrix}-CHCN\\[4pt]-CO\end{vmatrix} \rightarrow \underset{\begin{matrix}|\\COOH\end{matrix}}{\overset{\begin{matrix}CH_2COOH\\|\end{matrix}}{C_8H_{14}}}$$

$$C_{11}H_{16}O_4Ba = BaCO_3 + C_{10}H_{16}O.$$
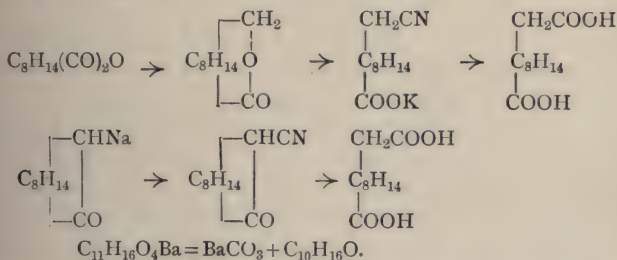
Since camphoric acid readily yields an anhydride when left in
contact with acetyl chloride even in the cold, it follows that it
must be a derivative of succinic acid or of glutaric acid, and a
choice can be made between the two alternatives by the following
considerations.   In the first place, camphoric acid contains only
one hydrogen atom in the α-position with regard to a carboxyl
group, for on bromination it yields a monobromo-camphoric acid,
and in the case of acids generally, it is known that it is only

possible to introduce as many bromine atoms into the molecule, as there are hydrogen atoms in the α-position. Again, camphoric anhydride in alcoholic solution, on treatment with ammonia, passes into α-camphoramic acid almost exclusively, the distillation of this acid then yielding camphorimide, which on hydrolysis by alkali hydroxides passes into β-camphoramic acid. These reactions show that there is a great difference in the reactivity of the carboxyl groups in camphoric acid, which may be accounted for by the fact that camphoric acid contains the grouping—

$$\begin{array}{c} CH.COOH \\ \vdots \\ C.COOH, \end{array}$$
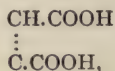
since the reactivity of carboxyl groups in aliphatic acids appears to be great or small accordingly as the adjacent carbon atom is hydrogenized or not.

$$\begin{array}{ccccc} CH.CO & & CH.CONH_2 & & CH.CO & & CH.COOH \\ \big| \quad \big| & \xrightarrow{NH_3} & \vdots & \to & \big| \quad NH & \xrightarrow{H_2O} & \vdots \\ \big| \quad O & & \vdots & & \big| & & \vdots \\ C.CO & & C.COOH & & C.CO & & C.CONH_2 \\ & \text{α-Camphoramic acid} & & & & \text{β-Camphoramic acid} \end{array}$$
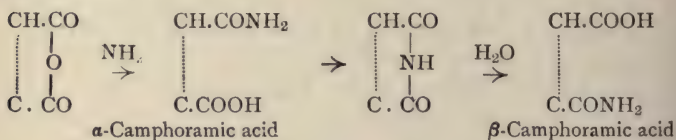
Still further evidence of the existence of the one hydrogen atom in the α-position is furnished by the fact that the bromination of homocamphoric acid yields an α-bromohomocamphoric acid from which, by heating the diethyl ester with quinoline, a dehydro-homocamphoric acid is obtained, the formation of this acid necessitating a hydrogen atom in the β-position in homo-camphoric acid, and hence in the α-position in camphoric acid.

$$\begin{array}{ccccccc} CH.COOH & & CH.CH_2.COOH & & CH.CHBr.COOH & & C:CH.COOH \\ \vdots & \to & \vdots & \to & \vdots & \to & \vdots \\ C.COOH & & C.COOH & & C.COOH & & C.COOH \end{array}$$
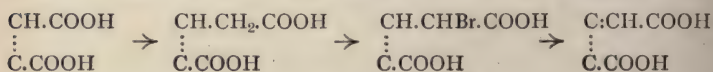
Camphor must also contain the grouping—

$$\begin{array}{c} C - C(CH_3)_2 - C(CH_3).C.C - \\ \big| \\ C \end{array}$$
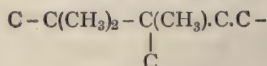
for on oxidation with nitric acid it yields camphoronic acid, $C_9H_{14}O_6$, which according to Bredt is an ααβ-trimethylcarballylic acid, since

on dry distillation it is decomposed into isobutyric and trimethyl-succinic acids, carbon dioxide, and carbon.

$$(CH_3)_2.C.COOH \\ | \\ 2\ CH_3.\overset{|}{C}.COOH\ =\ \overset{(CH_3)_2.C.COOH}{\underset{CH_3.CH.COOH}{|}} \rightarrow\ +\ 2\ (CH_3)_2CH.COOH + CO_2 + C \\ | \\ CH_2.COOH$$
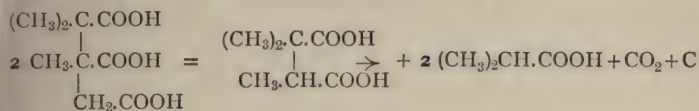
This structure for the acid was confirmed later by its synthesis by Perkin and Thorpe from aceto-acetic ester and α-bromoisobutyric ester, which condense in the presence of zinc to form ethyl-β-hydroxytrimethyl-glutarate. The hydroxyl group is successively replaced by chlorine and cyanogen, and the cyano-acid hydrolyzed by means of hydrochloric acid when camphoronic and trimethyl-glutaconic acids are simultaneously produced, the latter acid separating directly from the solution.

$$(CH_3)_2C.Br.COOR + CH_3.CO.CH_2.COOR \overset{Zn}{\longrightarrow}$$
$$(CH_3)_2C(COOR).C(OH)(CH_3).CH_2.COOR$$
$$\downarrow PCl_5$$
$$(CH_3)_2.C(COOR).C.Cl(CH_3).CH_2.COOR$$
$$\overset{KCN}{}$$
$$(CH_3)_2.C(COOR).C(CN)(CH_3).CH_2COOR \longleftarrow$$
$$\downarrow HCl$$
$$(CH_3)_2C(COOH).C(CH_3)(COOH).CH_2.COOH\ +$$
$$\qquad\qquad (CH_3)_2C.(COOH).C(CH_3):CH.COOH$$

Camphoronic acid   Trimethyl-glutaconic acid
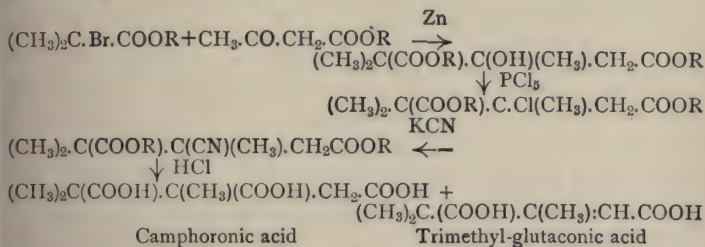
Again, it may be shown that the configuration of an α-methyl-ββ-dimethyl-glutaric acid exists in the camphor molecule, because camphoric acid, when oxidized with potassium permanganate, is converted into an acid, $C_8H_{12}O_5$ (Balbiano's acid), a dibasic acid in which the fifth oxygen atom does not function as ketonic, since only addition compounds are obtained on treatment with hydroxylamine and hydrazines. This acid may be reduced by hydriodic acid to another acid of composition $C_8H_{14}O_4$, from which, by oxidation, αββ-trimethyl-glutaric acid is obtained, a result which indicates that camphoric acid contains the grouping—

$$-C - C(CH_3) - C(CH_3)_2 - C - C -$$
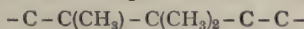
The fact that camphoric acid contains the cyclopentane ring is shown by the investigations of Lapworth (see p. 21), and also

by the conversion of bornyl chloride, on oxidation with nitric acid, into camphoric acid and apocamphoric acid, the latter acid being undoubtedly a cyclopentane derivative, as is shown by its synthesis by Komppa (see p. 19).

Chiefly from the study of the decomposition products of camphoronic acid, Bredt was led in 1893 to assign the following formulæ to camphor and camphoric acid :—

$$
\begin{array}{ll}
\begin{array}{l}
CH_2\!-\!CH\!-\!\!-\!\!-\!CH_2 \\
\quad\quad | \quad\quad\quad | \\
\quad\quad C.(CH_3)_2 \qukeleton | \\
\quad\quad | \quad\quad\quad | \\
CH_2\!-\!C(CH_3)\!-\!CO \\
\quad\quad\text{Camphor}
\end{array}
&
\begin{array}{l}
CH_2\!-\!CH\!-\!\!-\!\!-\!COOH \\
\quad\quad | \quad\quad\quad\quad | \\
\quad\quad C(CH_3)_2 \\
\quad\quad | \\
CH_2\!-\!C(CH_3)\!-\!COOH \\
\quad\text{Camphoric acid}
\end{array}
\end{array}
$$
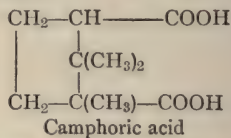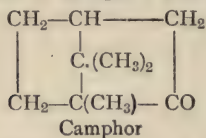
and these formulæ are largely justified by the facts noted in the preceding pages. Thus the oxidation of camphor may be illustrated—

$$
\begin{array}{l}
CH_2.CH\!-\!\!-\!\!-\!CH_2 \\
\quad\quad | \quad\quad\quad | \\
\quad\quad C(CH_3)_2 \\
\quad\quad | \\
CH_2.C(CH_3)\!-\!CO
\end{array}
\ \longrightarrow\
\begin{array}{l}
CH_2.CH.COOH \\
\quad\quad | \\
\quad\quad C(CH_3)_2 \\
\quad\quad | \\
CH_2.C(CH_3).COOH \\
\quad\text{Camphoric acid}
\end{array}
\ \longrightarrow\
\begin{array}{l}
COOH\ COOH \\
\quad\quad | \\
\quad\quad C(CH_3)_2 \\
\quad\quad | \\
CH_2\!-\!C(CH_3).COOH \\
\quad\text{Camphoronic acid}
\end{array}
$$
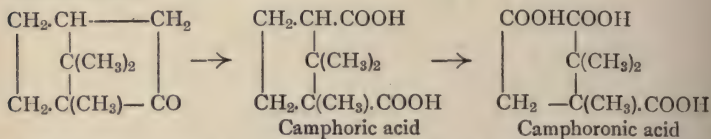
Further confirmation of the Bredt formula is given by the synthesis of racemic camphoric acid[1] by Komppa (see p. 22),

---

[1] Since the above was written, doubt seems to be cast on Komppa's work by the investigations of Blanc and Thorpe, who consider that the methyl diketocamphorate of Komppa is not, as he supposed, a *C*-methyl derivative, but is really an *O*-methyl ether, for on treatment with a large excess of aqueous alkaline hydroxide it yields methyl diketoapocamphoric acid, as is shown by the oxidation of this latter compound with potassium permanganate to $\beta\beta$-dimethyl glutaric acid.

$$
\begin{array}{l}
CO.CH(COOR) \\
\quad\quad | \\
\quad\quad C(CH_3)_2 \\
\quad\quad | \\
CO.C(CH_3).COOR
\end{array}
\qquad
\begin{array}{l}
CO\!-\!\!-\!\!-\!CH.COOR \\
\quad | \quad\quad\quad\quad | \\
\quad | \quad\quad\quad\quad C(CH_3)_2 \\
\quad | \quad\quad\quad\quad | \\
C(OCH_3)\!:\!C.COOR \\
\quad\text{Blanc and Thorpe} \\
\quad\quad\quad \downarrow KHO
\end{array}
$$

$$
\begin{array}{l}
HOOC.CH_2 \\
\quad\quad | \\
\quad\quad C(CH_3)_2 + \\
\quad\quad | \\
HOOC.CH_2
\end{array}
\begin{array}{l}
\\
COOH \\
| \\
COOH
\end{array}
\ \overset{O}{\longleftarrow}\
\begin{array}{l}
CO.CH.COOR \\
\quad\quad | \\
\quad\quad C(CH_3)_2 \\
\quad\quad | \\
CO.CH.COOR
\end{array}
$$
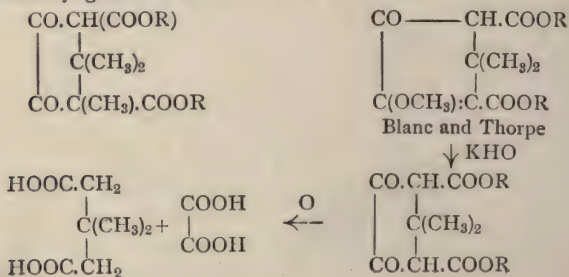
which renders that of camphor an accomplished fact, since camphoric anhydride may be converted into homocamphoric acid, and the distillation of the barium salt of this acid yields camphor (see above).

A further synthesis of camphor has been carried out by Wallach, who finds that nopinene (β-pinene), on saturation with a current of hydrogen chloride, yields a mixture of dipentene dihydro-chloride and bornyl chloride. The bornyl chloride is then converted into camphene, which in its turn can be transformed into isoborneol and camphor.

$$\begin{array}{ccc}
\text{—CH——CH}_2 & & \\
\text{CH}_2\ \text{C.(CH}_3)_2\ \text{CH}_2\ \xrightarrow{\text{HCl}} & \begin{array}{c}\text{CH}_2.\text{C(CH)}_3\text{—CHCl}\\ \mid\\ \text{C(CH}_3)_2\\ \mid\\ \text{CH}_2.\text{CH——CH}_2\end{array} & \xrightarrow{-\text{HCl}} \begin{array}{c}\text{CH}_2.\text{CH}\ .\ \text{C:CH}_2\\ \mid\quad\ \text{CH}_2\\ \mid\\ \text{CH}_2\text{—CH—C(CH}_3)_2\end{array}\\
\text{—CH——C:CH}_2 & & \downarrow \text{H}_2\text{SO}_4
\end{array}$$

$$\begin{array}{ccc}
\begin{array}{c}\text{CH}_2.\text{CH——CH}_2\\ \mid\\ \text{C(CH}_3)_2\\ \mid\\ \text{CH}_2.\text{C(CH}_3).\text{CO}\end{array} & \xleftarrow{\text{O}} & \begin{array}{c}\text{CH}_2.\text{CH.C(OH).CH}_3\\ \mid\quad\ \text{CH}_2\\ \mid\\ \text{CH}_2.\text{CH.C(CH}_3)_2\\ \text{Isoborneol}\end{array}
\end{array}$$
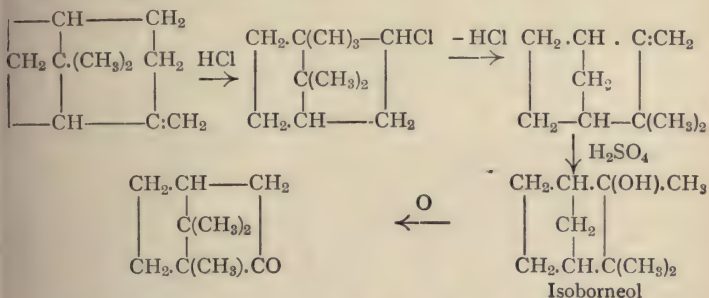
Objections may be raised to the above formula for camphor, since such a compound should apparently give thymol, $C_6H_3(C_3H_7)(OH)(CH_3)[1.2.4]$, whereas one actually gets carvacrol, $C_6H_3(C_3H_7)(OH)(CH_3)[1.3.4]$; again, it does not explain the conversion of α-campholytic acid into β-campholytic acid (isolauronolic acid)—

$$\begin{array}{ccccc}
\begin{array}{c}\text{CH}_2.\text{CH.COOH}\\ \mid\\ \text{C(CH}_3)_2\\ \mid\\ \text{CH}_2.\text{C(CH}_3).\text{COOH}\end{array} & \longrightarrow & \begin{array}{c}\text{CH}_2.\text{CH.COOH}\\ \mid\\ \text{C(CH}_3)_2\\ \mid\\ \text{CH}:\text{C.CH}_3\end{array} & \xrightarrow{\text{dil.\,H}_2\text{SO}_4} & \begin{array}{c}\text{CH}_2\text{CH}_2\\ \mid\\ \text{C(CH}_3)_2\\ \mid\\ \text{HOOC.C}:\text{C.CH}_3\end{array}\\
 & & \alpha\text{-Campholytic acid} & & \beta\text{-Campholytic acid}
\end{array}$$
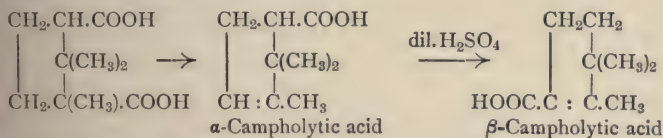
the structure of the β-acid having been confirmed by its synthesis

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Komppa has, however, repeated his work (*Jour. Chem. Soc.* 1911, **99**, 29), and insists that his views are correct, at the same time pointing out that Blanc and Thorpe's interpretation of the above ester as an *O*-methyl ester cannot hold, since the methyl group is not removed when the ester is boiled with hydriodic acid.

(p. 25), and that of the α-acid following from its oxidation to $\alpha\alpha$-dimethyltricarballylic acid,

$$HOOC.CH_2.CH(COOH).C(CH_3)_2.COOH.$$

A similar case is seen in the α- and β-campholenic acids, which result as nitriles from camphor-oxime by the action of dilute sulphuric acid and hydriodic acids respectively.
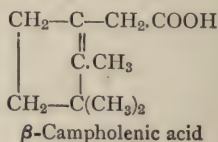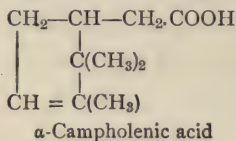
Perkin has recently (1911) obtained an isomer of camphor which he designates as *epicamphor*. This ketone is produced when camphane carboxylic acid (I) is brominated, the bromine replaced by the hydroxyl group, and the resulting hydroxy-acid (II), oxidized by lead peroxide.
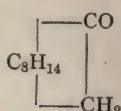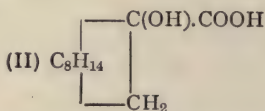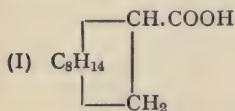
Epicamphor is readily volatile in steam and has the same odour as camphor. It melts at about 165° C. and closely resembles camphor in its properties.

By the reduction of camphor in alcoholic solution with sodium Wallach obtained the secondary alcohol borneol, which, however, was found to be mixed with more or less isoborneol. Tschugaeff showed that the mixture could be separated by the xanthogenic ester process, as only a small quantity of the ester of isoborneol is obtained, and may be removed by distillation in a current of steam, the main portion of the isoborneol not entering into reaction.

Since camphene may be converted into isoborneol by dissolving the hydrocarbon in glacial acetic acid, and heating the mixture with dilute sulphuric acid, there must evidently be a close relationship between the two compounds. Thus isoborneol appears to be a tertiary alcohol—

$$CH_2.CH.C:CH_2 \qquad \xrightarrow{H_2O} \qquad CH_2.CH.C(OH).CH_3$$

$$\mid \quad CH_2 \quad \mid \qquad\qquad \mid \quad CH_2 \quad \mid$$

$$CH_2.CH.C(CH_3)_2 \qquad\qquad CH_2.CH.C(CH_3)_2$$

Camphene   Isoborneol
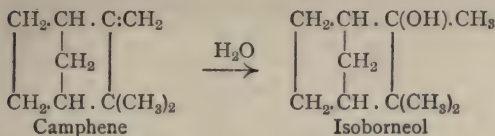
The genetic relations of camphor and its most important derivatives are shown in the following chart :—

Camphene → Isoborneol   Homocamphoric acid ← Campholide

Borneol   O   Cyancamphor   Camphoric anhydride

p-Cymene   P₂O₅

Carvacrol ← —— C A M P H O R ——→ Camphoric + Camphoronic acid   acid

Aminocamphor ←—— Isonitrosocamphor

HNO₂

Diazocamphor   Camphorquinone ——

Heat   O ↑ ↓ H

Camphenone   α-Oxycamphor

O   Trimethyl succinic acid + Isobutyric acid
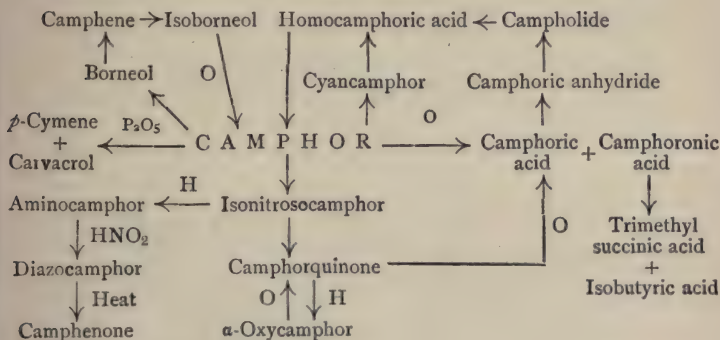
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Only the most important papers dealing with the various compounds mentioned in the text are referred to, and cross-references may be obtained in most cases from these. For fuller details, Heusler's "Terpenes," Wallach's "Die Terpene," Semmler's "Die Aetherische Oele," and Aschan's "Chemie d. Alicyklischen Verbindungen," should be consulted.

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CHAPTER III

THE URIC ACID OR PURINE GROUP

THE study of the members of this group of compounds has always been a fascinating one for chemists on account of the fact that many individual members are obtained as the products of animal and vegetable metabolism, and it has always seemed probable that a detailed investigation of the various substances under consideration might lead to a knowledge of the way in which the living organism was able to synthesize complicated derivatives from comparatively simple compounds.

One of the earliest researches on uric acid was that of Liebig and Wöhler in 1838, in which it was shown that the acid and its derivatives may be considered as derived from barbituric acid, $C_4H_4O_3N_2$, the ureide of malonic acid. These ureides may be considered as the acyl derivatives of urea, and many of them are obtained in the decomposition of uric acid and its derivatives, more particularly those which may be considered as derived from the condensation of one molecule of urea with one molecule of a dibasic acid, giving rise to cyclic ureides. Of these cyclic ureides one of the most important is *alloxan*, or mesoxalyl urea, obtained by the oxidation of uric acid with cold nitric acid.

$$C_5H_4N_4O_3 + H_2O + O = C_4H_2N_2O_4 + CO(NH_2)_2.$$
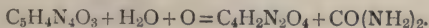
Alloxan is of considerable importance on account of its ready transformation into other ureides, some of which have been used in the synthetic production of uric acid and its derivatives. A synopsis of its more important decompositions is given in the chart below.

$$
\begin{array}{c}
\underset{\underset{\displaystyle NH_2}{|}}{\overset{\displaystyle NH_2}{|}} \quad \underset{\underset{\displaystyle COOH}{|}}{\overset{\displaystyle COOH}{|}} \\
CO \ + \ C(OH)_2 \xleftarrow{\ HotKHO\ }
\end{array}
\qquad
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CO \\
|\qquad| \\
NH\!-\!CO
\end{array}
\xrightarrow{\ Baryta\ }
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CO \\
|\qquad| \\
NH_2\ \ COOH \\
\text{Alloxanic acid}
\end{array}
$$

Reduction (H_2S)   Reduction (Zn, HCl, warm)

$$
\begin{array}{c}
NH\!-\!CO \qquad CO\!-\!\!-\!\!-\!NH \\
|\qquad\quad|\qquad\qquad\quad| \\
CO\quad CH\!-\!O\!-\!C(OH)\quad CO \\
|\qquad\quad|\qquad\qquad\quad| \\
NH\!-\!CO \qquad CO\!-\!\!-\!\!-\!NH \\
\text{Alloxantin}
\end{array}
$$

$$
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CH.OH \\
|\qquad| \\
NH\!-\!CO
\end{array}
$$
Dialuric acid (Tartronyl urea)

conc. H_2SO_4 at $100°$ C.

Fuming | HNO_3

$$
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CH_2 \\
|\qquad| \\
NH\!-\!CO
\end{array}
$$
Barbituric acid

$$
\xrightarrow{}
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CH.NO_2 \\
|\qquad| \\
NH\!-\!CO
\end{array}
$$
Dilituric acid

HNO_2.

Reduction

HNO_2

NH_2OH

$$
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad C\!:\!NOH \\
|\qquad| \\
NH\!-\!CO
\end{array}
$$
Violuric acid

Reduction

$$
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CHNH_2 \\
|\qquad| \\
NH\!-\!CO
\end{array}
$$
Uramil (Dialuramide)

Alloxan on oxidation with warm dilute nitric acid passes into parabanic acid (oxalyl urea) $C_3H_2O_3N_2$

$$
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad CO \\
|\qquad| \\
NH\ +\ CO
\end{array}
\ +\ O\ =\ CO_2\ +\
\begin{array}{c}
NH\!-\!CO \\
|\qquad| \\
CO\quad| \\
|\qquad| \\
NH\!-\!CO
\end{array}
$$
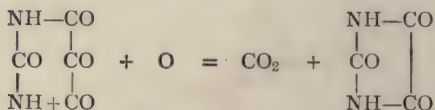
The ureides readily hydrolyze, yielding, according to conditions, either a ureido-acid (see alloxanic acid above), or urea and a dibasic acid. The majority are more or less strong acids, in which, since they do not contain a carbonyl group, one must assume that the acid character depends upon the presence of

replaceable hydrogen in the imino-groups, the acidic nature of which is determined by the adjacent carbonyl groups.

Alloxan combines directly with dialuric acid to form alloxantin, $C_8H_4O_7N_4.3H_2O$, a compound in which one of the water molecules is probably to be considered as constitutional. This substance crystallizes in small prisms, which turn red on exposure to air containing ammonia, owing to their conversion into murexide (ammonium purpurate), $C_8H_4(NH_4)N_5O_6$, a substance also formed when uric acid is evaporated to dryness with dilute nitric acid and the residue moistened with ammonia, this reaction being known as the "*murexide*" *test* for uric acid. Murexide has recently been investigated by Hartley, who has obtained it by the action of ammonia on alloxantin at 100° C., the decomposition probably proceeding thus :—

$$
\begin{array}{ccc}
\begin{array}{ll}
NH.CO & CO-NH \\
| \ \ | & | \ \ | \\
CO \ CH.O.C(OH)CO \\
| \ \ | & | \ \ | \\
NH.CO & CO-NH
\end{array}
& \xrightarrow{NH_3} &
\begin{array}{ll}
NH.CO & CO-NH \\
| \ \ | & | \ \ | \\
CO \ CH.NH.C(OH) CO \\
| \ \ | & | \ \ | \\
NH.CO & CO-NH
\end{array}
\end{array}
$$

$$\downarrow NH_3$$

$$
\begin{array}{ll}
NH.CO & CO.NH \\
| \ \ | & | \ \ | \\
CO \ C-N=C \ \ CO \\
| \ \ \| & | \ \ | \\
NH.C(ONH_4)CO.NH
\end{array}
$$
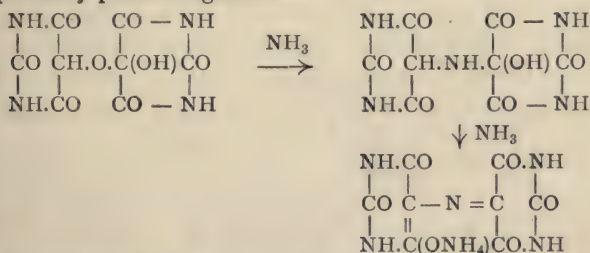
and also by the action of alcoholic ammonia at 73° C. on alloxan, the first steps in the reaction probably leading to the oxidation of the alcohol to aldehyde and the consequent reduction of some of the alloxan to tartronyl urea, which then unites with the unaltered alloxan to yield alloxantin, when the reaction proceeds as above.

$$
\begin{array}{ll}
NH-CO \\
| \ \ \ | \\
CO \ \ C(OH)_2 \\
| \ \ \ | \\
NH-CO
\end{array}
\xrightarrow{C_2H_6O}
C_2H_4O +
\begin{array}{ll}
NH-CO \\
| \ \ \ | \\
CO \ \ CH(OH) \\
| \ \ \ | \\
NH-CO
\end{array}
\xrightarrow{alloxan}
alloxantin.
$$
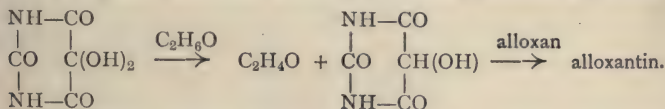
Among other ureides which are obtained by the decomposition of uric acid and its derivatives may be mentioned dimethyl alloxan, $C_4(CH_3)_2O_4N_2$, obtained by the oxidation of caffeine with nitric acid, tetramethyl alloxantin (amalic acid), $C_8(CH_3)_4O_7N_4$, formed when caffeine is oxidized with potassium chlorate and

hydrochloric acid, parabanic acid (oxalyl urea), $C_3H_2O_3N_2$, formed in the alkaline oxidation of uric acid, dimethyl parabanic acid, $C_3(CH_3)_2O_3N_2$, a product of the oxidation of caffeine with chlorine water, and allantoin, $C_4H_6O_3N_4$, obtained when uric acid is oxidized by lead peroxide, manganese dioxide, etc.

$$C_5H_4N_4O_3 + H_2O + O = CO_2 + C_4H_6N_4O_3.$$
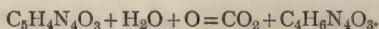
Allantoin is the di-ureide of glyoxylic acid, its constitution being determined by its synthetical formation when glyoxylic acid and urea are heated together for some hours at 100° C.

$$
\begin{array}{ccccccc}
NH_2 & HO.CH.OH & H_2N & & & & NH.CH.NH.CONH_2 \\
| & | & | & & & & | \\
CO & + & | & + & CO & = & 2H_2O & + & CO & | \\
| & | & | & & & & | \\
NH_2 & OCOH & NH_2 & & & & NH.CO
\end{array}
$$
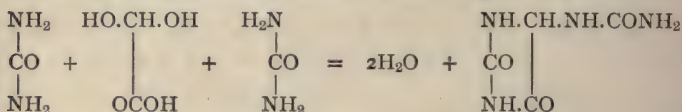
On standing with concentrated caustic potash it yields allantoic acid, whilst if heated for some time with water it yields urea and allanturic acid.

$$
\begin{array}{ccc}
NH.CH.NHCONH_2 & NH.CH.NHCONH_2 & NH_2 \quad NH.CHOH \\
| & \leftarrow \quad | & \rightarrow \quad | \qquad | \\
CO \quad | & CO \quad | & CO + CO \quad | \\
| & | & | \qquad | \\
NH_2 \; COOH & NH.CO & NH_2 \quad NH.CO \\
\text{Allantoic acid} & & \text{Allanturic acid}
\end{array}
$$
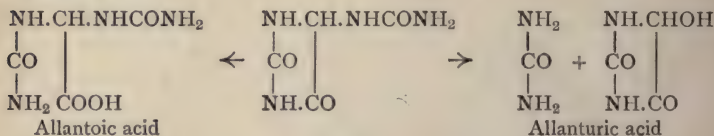
In the course of his investigations on the ureides, Baeyer found that uramil or aminobarbituric acid combined with potassium cyanate to form a salt of an acid, which he called *pseudo-uric acid*.

$$
\begin{array}{ccc}
NH—CO & & NH—CO \\
| \qquad | & \xrightarrow{KCNO} & | \qquad | \\
CO \quad CHNH_2 & & CO \quad CHNHCONHK \\
| \qquad | & & | \qquad | \\
NH—CO & & NH—CO
\end{array}
$$

$$\downarrow \text{acid}$$

$$
\begin{array}{c}
NH—CO \\
| \qquad | \\
CO \quad CHNHCONH_2 \\
| \qquad | \\
NH—CO
\end{array}
$$
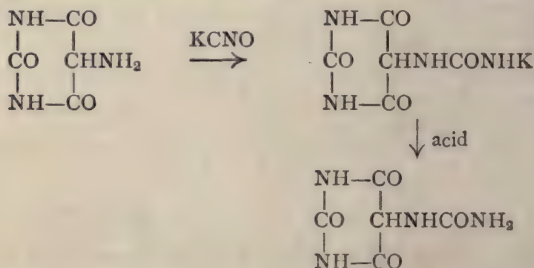
This acid differs from uric acid in containing the elements of one molecule of water more than uric acid (*i.e.* $C_5H_6N_4O_4$ as against

$C_5H_4N_4O_3$), and Baeyer considered that if the pseudo-uric acid could be made to lose one molecule of water it would pass into uric acid, and from the resulting analogy between urea and cyanamide he gave as the formula for uric acid.

$$\begin{array}{l} NH-CO \\ | \quad\quad | \\ CO \quad CH-NH-C\equiv N. \\ | \quad\quad | \\ NH-CO \end{array}$$
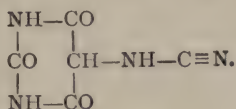
He was, however, not successful in his attempts to synthesize uric acid in this way, and his formula was not generally accepted.

Very little work was done on the group in the few succeeding years, although Fittig in his " Traité d. Chem. organique " proposed the following formula for uric acid :—
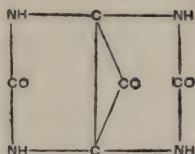
whilst Medicus in 1875 gave as an alternative :—

$$\begin{array}{l} NH.CO \\ | \quad\quad | \\ CO \quad C-NH \\ | \quad\quad\quad | \\ | \quad\quad || \quad CO \\ | \quad\quad\quad | \\ NH.C-NH \end{array}$$
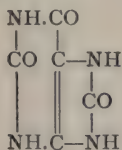
advancing as reasons that uric acid on hydrolysis with mineral acids yields amino-acetic acid, ammonia and carbon dioxide, whilst on oxidation with nitric acid it yields alloxan and urea, and with alkaline potassium permanganate solution it yields allantoin, which readily hydrolyzes to urea and glyoxylic acid.   Making use also of earlier observations of Strecker and other investigators, who showed that nitrous acid converted guanine into xanthine, and that the methylation of theobromine yielded caffeine, Medicus proposed the following formulæ for these substances :—

$$NH.CO$$
$$HN:C \quad C—NH$$
$$\qquad \qquad CH$$
$$NH.C \, . \, N$$
Guanine

$$NH.CO$$
$$CO \quad C—NH$$
$$\qquad \qquad CH$$
$$NH.C—N$$
Xanthine

$$CH_3N — CO$$
$$CO \quad C—NH$$
$$\qquad \qquad CH$$
$$CH_3N — C—N$$
Theobromine

$$CH_3N — CO$$
$$CO \quad C—NCH_3$$
$$\qquad \qquad CH$$
$$CH_3N — C—N$$
Caffeine
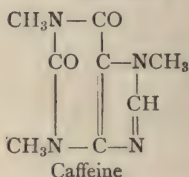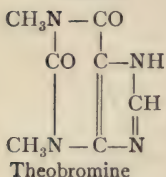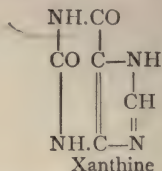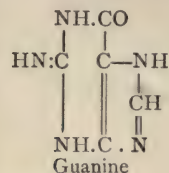
Here the matter rested for several years until in 1882 Emil Fischer published an elaborate investigation on caffeine, which may be said to have given the first insight into the true nature of the grouping in these substances. Earlier investigators had shown that oxidation of caffeine, under varying conditions, had given rise to dimethyl parabanic acid, and to tetramethyl alloxantin, whilst hydrolysis with baryta water had yielded *caffeidine*, $C_7H_{12}ON_4$, which could be further broken down into ammonia, carbon dioxide, methylamine and sarcosine

$$C_7H_{12}ON_4 + 5H_2O = NH_3 + CO_2 + 2CH_3NH_2 + HCOOH$$
$$+ CH_3NH.CH_2COOH.$$
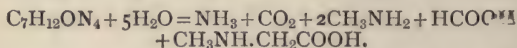
These observations were confirmed by Fischer, who further found that the oxidation of caffeine with chlorine water yielded monomethyl urea and dimethyl alloxan, thus showing that there are three methyl groups present in the caffeine molecule. Again, caffeine may be brominated and the bromo-compound on treatment with alcoholic potash yields ethoxy-caffeine, which on hydrolysis with dilute hydrochloric acid is converted into hydroxy-caffeine.

$$C_8H_{10}N_4O_2 \rightarrow C_8H_9BrN_4O_2 \rightarrow C_8H_9(OC_2H_5)N_4O_2 \rightarrow C_8H_9(OH)N_4O_2.$$
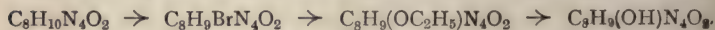
This hydroxy-caffeine behaves as an unsaturated compound combining directly with one molecule of bromine to form a product which by the action of alcoholic potash exchanges its bromine for ethoxy-groups, and is transformed into diethoxy-hydroxy-caffeine.

$$C_8H_9(OH)N_4O_2 \rightarrow C_8H_9Br_2(OH)N_4O_2 \rightarrow C_8H_9(OC_2H_4)_2.(OH).N_4O_2.$$
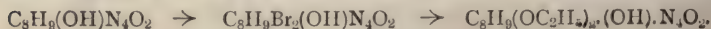
Now on hydrolysis with concentrated hydrochloric acid, this substance decomposes, the action proceeding in two directions,

$$C_8H_9(OC_2H_5)_2.(OH)N_4O_2 + 2H_2O \left\{ \begin{array}{l} \rightarrow 2C_2H_5OH + CH_3NH_2 + C_7H_7N_3O_5 \\ \qquad\qquad\qquad\qquad\qquad\text{Apocaffeine} \\ \rightarrow 2C_2H_5OH + CH_3NH_2 + CO_2 + \\ \qquad\qquad\quad C_6H_7N_3O_3 \quad \text{Hypocaffeine} \end{array} \right.$$
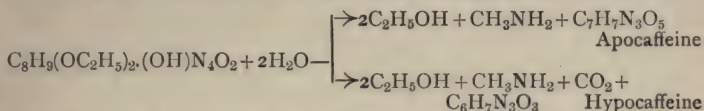
and it is from the products of fission of these two substances that one arrives at an idea of the structure of the caffeine molecule. Apocaffeine when boiled with water passes into caffuric acid, $C_6H_9N_3O_4$, and this on hydrolysis with basic lead acetate yields methylamine, monomethyl urea, and mesoxalic acid.

$$C_7H_7N_3O_5 \overset{H_2O}{\rightarrow} CO_2 + C_6H_9N_3O_4 \overset{3H_2O}{\rightarrow} \begin{array}{l} CH_3NH_2 + H_2N.CO.NHCH_3 \\ + (HO)_2.C(COOH)_2 \end{array}$$
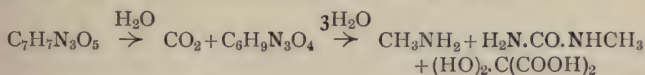
On reduction with hydriodic acid, caffuric acid yields hydrocaffuric acid, $C_6H_9N_3O_3$, which, on hydrolysis with caustic baryta, decomposes into methylamine, carbon dioxide, and methylhydantoin.

$$C_6H_9N_3O_4 \overset{HI}{\rightarrow} C_6H_9N_3O_3 \overset{H_2O}{\rightarrow} CH_3NH_2 + CO_2 + \begin{array}{c} N(CH_3).CH_2 \\ | \qquad\quad | \\ CO \qquad | \\ | \qquad\quad | \\ NH - CO \end{array}$$
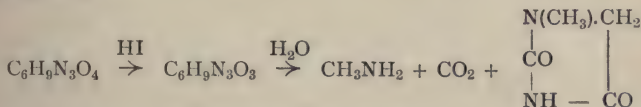
Thus it will be recognized that hydrocaffuric and caffuric acids, apocaffeine and caffeine must contain the grouping

$$\begin{array}{c} C^* \\ | \\ C-NCH_3 \\ | \qquad\quad | \\ | \qquad\quad C \\ | \qquad\quad | \\ C-C \end{array}$$
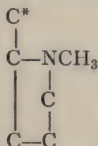
in order to account for these various decomposition products, C^* representing the carbon atom which is eliminated as carbon dioxide. The decomposition of hypocaffeine throws further light on the subject. This substance, when boiled with water, loses carbon dioxide, and yields caffolin, $C_5H_9N_3O_2$, the latter substance, on oxidation with potassium ferricyanide, being converted into monomethyl urea and methyloxamic acid, whilst if potassium

permangate be used as oxidant, it is transformed into dimethyl oxamide, carbon dioxide, and ammonia.

$$C_6H_7N_3O_3 \xrightarrow{H_2O} CO_2 + C_5H_9N_3O_2 - \begin{cases} \longrightarrow NH_2.CO.NHCH_3 + \overset{\displaystyle CONHCH_3}{\underset{\displaystyle COOH}{|}} \\ \longrightarrow \overset{\displaystyle CONHCH_3}{\underset{\displaystyle CONHCH_3}{|}} + CO_2 + NH_3 \end{cases}$$
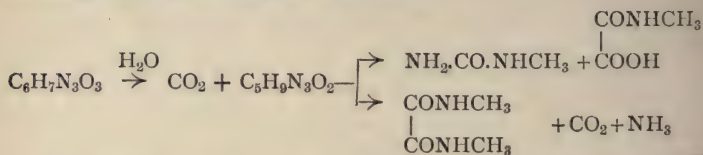
Thus caffolin contains the grouping :—

$$\begin{array}{c} C - : - NCH_3 \\ | \quad - | - \\ | \quad \quad C \\ | \quad \quad | \\ CH_3N.C - : - N \end{array}$$
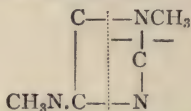
the dotted lines showing the different courses of the oxidation.

Consequently, caffolin must be either

$$\text{(I)} \quad \begin{array}{c} CH_3NHCO.HC - NCH_3 \\ | \quad \quad \quad | \\ HN - CO \end{array} \quad \text{or} \quad \begin{array}{c} HO.CH.N.CH_3 \\ | \quad \quad CO \\ CH_3NH.C : N \end{array} \quad \text{(II)}$$
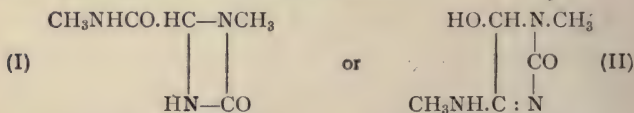
the former being excluded on account of the relation of caffolin to hydrocaffuric acid, which, as shown above, must contain the grouping (II). Thus, since caffeine yields dimethyl alloxan and monomethyl urea, beside the above products, one has the following groupings to connect together :—

$$\begin{array}{c} C \\ | \\ C - NCH_3 \\ | \quad \quad | \\ | \quad \quad C \\ | \quad \quad | \\ C - N \end{array} \qquad \begin{array}{c} C - NCH_3 \\ | \quad \quad | \\ \quad \quad C \\ \quad \quad | \\ CH_3N.C - N \end{array} \qquad \begin{array}{c} CH_3N - C \\ | \quad \quad | \\ C \quad \quad C \\ | \quad \quad | \\ CH_3N - C \end{array}$$
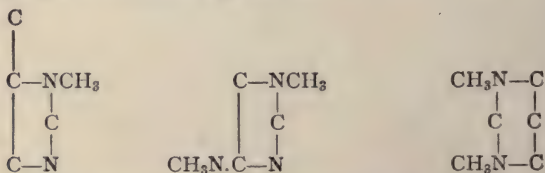
and the caffeine skeleton must consequently be

$$\begin{array}{c} CH_3N - C \\ | \quad \quad | \\ C \quad C - NCH_3 \\ | \quad \quad \quad | \\ | \quad \quad \quad C \\ | \quad \quad \quad | \\ CH_3.N - C - N \end{array}$$
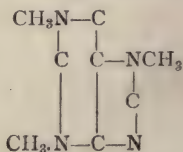
and Fischer first gave as the structural formula for caffeine, the following :—

$$
\begin{array}{c}
CH_3N\!-\!CH \\
|\quad\; \| \\
CO\;\; C\!-\!NCH_3 \\
|\quad\quad | \\
|\quad\quad CO \\
|\quad\quad | \\
CH_3N\!-\!C\!=\!N
\end{array}
$$
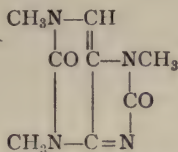
a view which he afterwards modified in 1897, when he prepared trimethylpseudo-uric acid, which he found on dehydration passed into hydroxycaffeine. This reaction shows that uric acid and caffeine contain the same carbon chain, which would not be the case if the above structure were correct. The corrected formula for caffeine is

$$
\begin{array}{c}
CH_3N\!-\!CO \\
|\quad\; | \\
CO\;\; C\!-\!NCH_3 \\
|\quad\quad | \\
|\quad\quad CH \\
|\quad\quad \| \\
CH_3N\!-\!C\!-\!N
\end{array}
$$
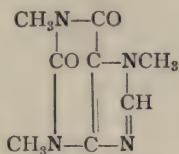
(see synthesis later). The earlier formula shown above was chiefly given on account of the fact that the direct methylation of the silver salt of hydroxycaffeine did not give a compound identical with tetramethyl uric acid.

From a chronological point of view the next synthetic work in this group was the synthesis of uric acid by Horbaczewski on heating amino-acetic acid for some time to 250° C. with a large excess of urea,

$$NH_2.CH_2.COOH + 3CO(NH_2)_2 = 3NH_3 + 2H_2O + C_5H_4N_4O_3,$$
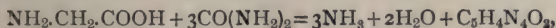
and also by heating urea with β-trichlorolactamide.

$$CCl_3.CHOH.CONH_2 + 2CO(NH_2)_2 = 3HCl + NH_3 + CO_2 + C_5H_4N_4O_3.$$
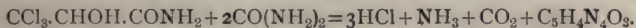
These two methods are both unsatisfactory, very small quantities of uric acid being obtained. A much more elegant but somewhat involved synthesis was, however, worked out somewhat later (1885) by Behrend, who showed that on leaving aceto-acetic ester in contact with urea in vacuo, over sulphuric acid, a β-uramido-crotonic ester is obtained, which, if its alkaline solution

be saturated with carbon dioxide, is converted into methyl uracil. This methyl uracil in contact with concentrated nitric acid undergoes simultaneous oxidation and nitration, yielding a nitro-uracil carboxylic acid which, when boiled with water, loses carbon dioxide, and is transformed into nitro-uracil.

$$
\begin{array}{ccc}
\begin{array}{c}
\mathrm{ROOC} \quad\quad \mathrm{H_2N} \\
| \qquad\qquad | \\
\mathrm{CH} \;+\; \mathrm{CO} \;\rightarrow \\
\| \qquad\qquad | \\
\mathrm{CH_3.C.OH} \quad \mathrm{HNH}
\end{array}
&
\begin{array}{c}
\mathrm{ROOC - NH} \\
| \qquad | \\
\mathrm{CH \quad CO} \;\rightarrow \\
\| \qquad | \\
\mathrm{CH_3.C - NH}
\end{array}
&
\begin{array}{c}
\mathrm{CO.NH} \\
| \qquad | \\
\mathrm{CH \quad CO} \\
\| \qquad | \\
\mathrm{CH_3.C - NH} \\
\text{Methyl uracil} \\
\downarrow \; \mathrm{HNO_3}
\end{array}
\end{array}
$$

$$
\begin{array}{ccc}
\begin{array}{c}
\mathrm{CO.NH} \\
| \qquad | \\
\mathrm{NO_2.C \quad CO} \\
\| \qquad | \\
\mathrm{HC - NH}
\end{array}
&
\leftarrow
&
\begin{array}{c}
\mathrm{CO.NH} \\
| \qquad | \\
\mathrm{NO_2.C \quad CO} \\
\| \qquad | \\
\mathrm{HOOC.C - NH}
\end{array}
\end{array}
$$
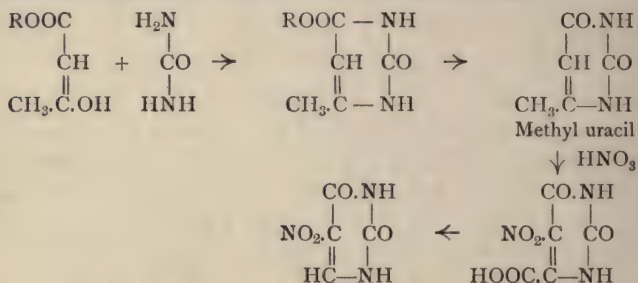
Nitro-uracil on reduction with tin and hydrochloric acid is converted into amido-uracil, the reaction proceeding somewhat further, the amino group being replaced by a hydroxyl group, and a hydroxy-uracil being simultaneously formed. This hydroxy-uracil (or isobarbituric acid) on further oxidation with bromine water yields a dihydroxy-uracil (isodialuric acid) which condenses readily with urea, in the presence of concentrated sulphuric acid, to form the desired uric acid.

$$
\begin{array}{ccc}
\begin{array}{c}
\mathrm{NH.CO} \\
| \qquad | \\
\mathrm{CO \quad C.NO_2} \;\rightarrow \\
| \qquad \| \\
\mathrm{NH.CH}
\end{array}
&
\begin{array}{c}
\mathrm{NH.CO} \\
| \qquad | \\
\mathrm{CO \quad C.NH_2} \;+ \\
| \qquad \| \\
\mathrm{NH.CH}
\end{array}
&
\begin{array}{c}
\mathrm{NH.CO} \\
| \qquad | \\
\mathrm{CO \quad C.OH} \\
| \qquad \| \\
\mathrm{NH.CH} \\
\downarrow \mathrm{O}
\end{array}
\end{array}
$$

$$
\begin{array}{ccc}
\begin{array}{c}
\mathrm{NH - CO} \\
| \qquad | \\
\mathrm{CO \quad C - NH} \\
| \qquad \| \quad \mathrm{CO} \\
| \qquad \| \quad | \\
\mathrm{NH - C - NH}
\end{array}
&
\begin{array}{c}
\text{urea} \\
\xleftarrow{\quad\quad} \\
\mathrm{H_2SO_4}
\end{array}
&
\begin{array}{c}
\mathrm{NH.CO} \\
| \qquad | \\
\mathrm{CO \quad C.OH} \\
| \qquad \| \\
\mathrm{NH.C.OH}
\end{array}
\end{array}
$$
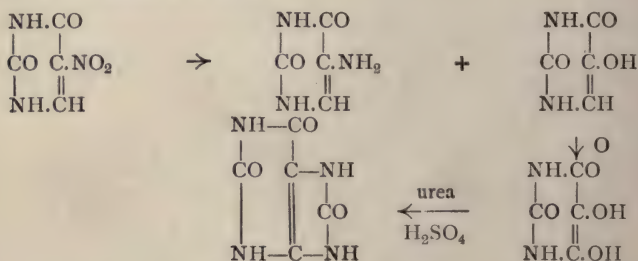
This synthesis of uric acid, of course, points to the validity of the Medicus formula as against that of the Fittig formula, and further confirmation of the former is given by an examination of the mono-methyl uric acids. The formula of Fittig (p. 105) is

symmetrical, and would allow of only one mono-methyl uric acid, whilst that of Medicus would allow of four isomers.   Hill in 1876 obtained a mono-methyl uric acid, which on oxidation yielded mono-methyl alloxan and urea, whilst Fischer in 1884 prepared a methyl uric acid, which on oxidation yielded alloxan and mono-methyl urea, showing that in this latter case methylation has taken place outside the alloxan ring.   This latter result would be impossible in the case of the Fittig formula, and hence the Fittig formula is incorrect and the Medicus formula is shown to be correct, both from the synthetic formation of uric acid, either by Behrend's method or Fischer's method (see below), and also from the fact that the four isomeric mono-methyl uric acids are all known.

The next great steps in the investigation of the compounds of the uric acid group were the classical researches of Emil Fischer, extending over a period from 1895 to 1900, in which he showed how these substances were inter-related and might be synthesized. To indicate the relationship of all the compounds of the group, Fischer calls the parent substance *Purine*, and assigns to it the following structural formula :—

$$
\begin{array}{c}
\quad\quad\quad 6 \\
1 \quad N = CH \\
\quad\quad | \quad\quad | \\
2 \quad CH \; 5 \; C-NH \quad 7 \\
\quad\quad || \quad\quad | \\
\quad\quad || \quad\quad || \quad CH \quad 8 \\
\quad\quad || \quad\quad || \\
3 \quad N - C - N \quad\quad 9 \\
\quad\quad\quad 4
\end{array}
$$
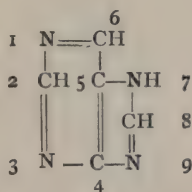
the ring being numbered as shown, to indicate the position of substituents.   The first synthesis effected by Fischer was that of uric acid itself, from the pseudo-uric acid of Baeyer (p. 104). This may be dehydrated by heating to about 185° C. with anhydrous oxalic acid, or as was shown later (1897) by boiling it with about five hundred times its weight of 20 *per cent.* hydrochloric acid for about a quarter of an hour, and concentrating the liquid to a small bulk, when the uric acid crystallizes out.

$$
\begin{array}{ccc}
\text{NH.CO} & & \text{NH.CO} \\
| \quad | & & | \quad | \\
\text{CO} \quad \text{CH.NH.CO.NHH} & \longrightarrow \quad H_2O \;+\; & \text{CO} \quad \text{C—NH} \\
| \quad | & & | \qquad\quad | \\
& & \qquad\quad \text{CO} \\
| \quad | & & | \qquad\quad | \\
\text{NH.CO} & & \text{NH—C—NH}
\end{array}
$$
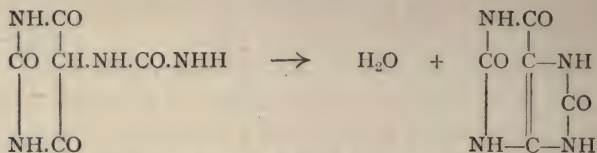
Thus uric acid appears as the keto-form of 2.6.8-trihydroxypurine, the keto-enolic form of tautomerism being characteristic of this series of compounds containing the – NH – CO – grouping, since they behave in some reactions as ketonic derivatives, and in others as hydroxylic compounds.

Purine itself was isolated a little later, in the following manner. Potassium urate, on being heated for some time with phosphorus oxychloride, yields at first 2.6-dichloro-8-oxypurine, which is finally converted into 2.6.8-trichloropurine. Hydriodic acid partially reduces this and at the same time replaces the chlorine atoms at 2 and 6, the resulting 2.6-di-iodopurine, on treatment with zinc dust and water, forming a zinc double salt, which is broken up by sulphuretted hydrogen with precipitation of zinc sulphide, whilst the purine goes into solution, and may be recovered by concentration of the solution. Thus we have

$$
\begin{array}{ccc}
\text{N = C.OH} & \text{N = C.Cl} & \text{N = C.Cl} \\
| \qquad | & | \qquad | & | \qquad | \\
\text{HO.C} \quad \text{C—NH} & \text{Cl.C} \quad \text{C—NH} & \text{Cl.C} \quad \text{C—NH} \\
\| \qquad | & \| \qquad | & \| \qquad \| \\
\qquad\quad \text{C.OH} & \qquad\quad \text{C.OH} & \qquad\quad \text{C.Cl} \\
\| \qquad \| & \| \qquad \| & \| \qquad \| \\
\text{N — C — N} & \text{N — C — N} & \text{N — C — N}
\end{array}
$$

Enolic form of Uric acid

$$
\begin{array}{cc}
\text{N = CH} & \text{N = CI} \\
| \qquad | & | \qquad | \\
\text{CH} \quad \text{C—NH} & \text{IC} \quad \text{C—NH} \\
\| \qquad | & \| \qquad | \\
\qquad\quad \text{CH} & \qquad\quad \text{CH} \\
\| \qquad \| & \| \qquad \| \\
\text{N — C — N} & \text{N — C — N}
\end{array}
$$
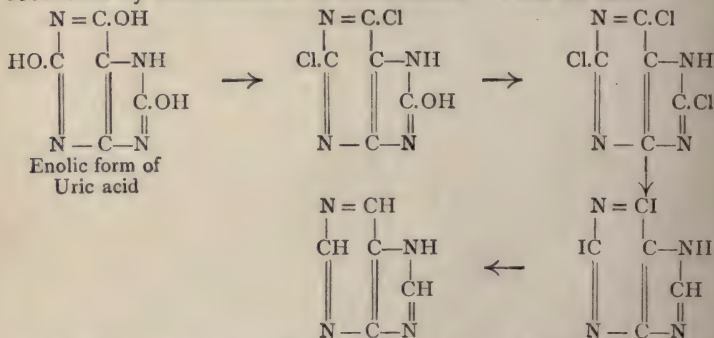
Since xanthine possesses the empirical formula $C_5H_4N_4O_2$, and uric acid is $C_5H_4N_4O_3$, it seemed probable that by reduction of the latter one might arrive at xanthine. Numerous attempts were made to carry out this reduction, but none of them were successful, the ultimate synthesis of xanthine from uric acid being due to Fischer in 1897.

But it is necessary here to make a slight digression. Caffeine is a trimethyl xanthine, and Fischer, as the result of his earlier work on caffeine, had come to the conclusion that it (and consequently xanthine) possessed a different carbon chain to that of uric acid, the two being represented thus—

$$
\begin{array}{cc}
-\text{CH} & -\text{CO} \\
\parallel & \mid \\
\text{C}- & \text{C}- \\
\mid & \parallel \\
\text{C}= & \text{C}- \\
\text{Caffeine} & \text{Xanthine}
\end{array}
$$
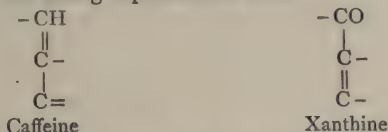
In an examination, however, of 1.3.-7-trimethyl pseudo-uric acid, he found that on dehydration it yielded a compound identical with hydroxy-caffeine, consequently hydroxy-caffeine is a trimethyl-uric acid, and hence caffeine and also xanthine must possess the same skeletal structure as that observed in uric acid. A further proof of this is given by the fact that the methylation of an aqueous alkaline solution of hydroxycaffeine yields tetramethyl-uric acid identical with that obtained by the direct methylation of uric acid itself. This result, of course, led Fischer to modify his original views as to the structure of caffeine, and as a result he assigned to it the following constitution :—

$$
\begin{array}{c}
\text{CH}_3.\text{N}-\text{CO} \\
\mid \qquad \mid \\
\text{CO} \quad \text{C}-\text{NCH}_3 \\
\mid \qquad \parallel \quad \mid \\
\qquad \quad \text{CH} \\
\mid \qquad \parallel \\
\text{CH}_3\text{N}-\text{C}-\text{N}
\end{array}
$$
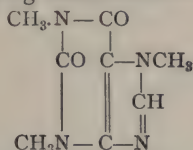
the correctness of which was shown by its synthesis from chlorotheophylline and from dimethyl alloxan. In the first method, dimethyl urea on condensation with malonic acid yields dimethylbarbituric acid, which reacts with nitrous acid to form dimethylvioluric acid, reduction of the latter yielding dimethyl-uramil. This readily combines with potassium cyanate to form dimethyl pseudo-uric acid, which on dehydration is converted into 1.3(δ)-dimethyl uric acid. This acid, on treatment with phosphorus pentachloride, is converted into chlorotheophylline, and the chloro-compound, on reduction with hydriodic acid and phosphonium iodide, passes into theophylline, which on methylation is transformed into caffeine.

8

$$
\begin{array}{ccccc}
CH_3NH & & CH_3.N{-}CO & & CH_3.N{-}CO \\
| & & | \quad | & HONO & | \quad | \\
CO & \rightarrow & CO \quad CH_2 & \rightarrow & CO \quad C{:}NOH \\
| & & | \quad | & & | \quad | \\
CH_3NH & & CH_3.N{-}CO & & CH_3.N{-}CO
\end{array}
$$

$$
\begin{array}{ccc}
 & CH_3.N{-}CO & CH_3.N{-}CO \\
H & | \quad | & | \quad | \\
\rightarrow & CO \quad CH.NH_2 \rightarrow & CO \quad CH.NH \\
 & | \quad | & | \quad | \quad | \\
 & CH_3.N{-}CO & CH_3.N{-}CO \quad CO.NH_2
\end{array}
$$

$$
\begin{array}{cccc}
CH_3N{-}CO & CH_3N{-}CO & CH_3N{-}CO & CH_3N{-}CO \\
| \quad | & | \quad | & | \quad | & | \quad | \\
CO \quad C{-}NCH_3 & CO \quad C{-}NH & CO \quad C{-}NH & CO \quad C{-}NH \\
| \quad \| & | \quad \| & | \quad \| & | \quad | \\
CH \leftarrow & CH \leftarrow & C.Cl \leftarrow & CO \\
| \quad \| & | \quad \| & | \quad \| & | \quad | \\
CH_3N{-}C{-}N & CH_3N{-}C{-}N & CH_3N{-}C{-}N & CH_3N{-}C{-}NH \\
\textbf{Caffeine} & & \textbf{Chlorotheophylline} &
\end{array}
$$
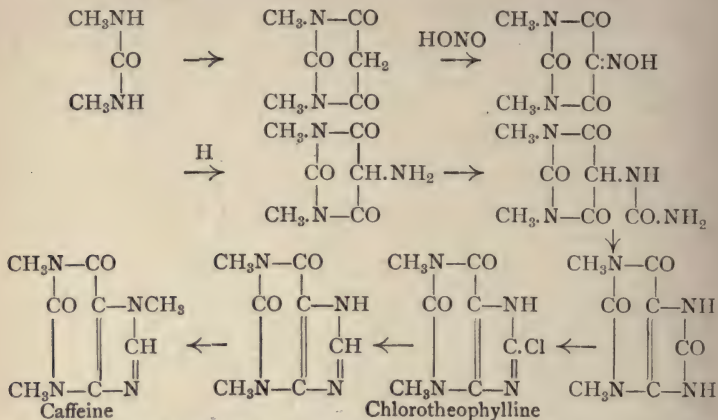
In the second method, dimethyl alloxan was left in contact with methylamine and an aqueous solution of sulphur dioxide, a trimethyl thionuric acid being formed, which on hydrolysis was converted into 1.3.7-trimethyl uramil. This uramil on treatment with potassium cyanate and dehydration in the usual manner yielded hydroxycaffeine (1.3.7)-trimethyl-uric acid. Chlorination and subsequent reduction of the latter compound then gave caffeine.

$$
\begin{array}{ccc}
CH_3.N{-}CO & & CH_3.N{-}CO \\
| \quad | & NH_2CH_3 & | \quad | \\
CO \quad CO & \xrightarrow{SO_2+H_2O} & CO \quad C(NHCH_3).SO_3H \\
| \quad | & & | \quad | \\
CH_3.N{-}CO & & CH_3.N{-}CO
\end{array}
$$

$$
\begin{array}{ccc}
CH_3N{-}CO & CH_3.N{-}CO & CH_3.N{-}CO \\
| \quad | & | \quad | & | \quad | \\
CO \quad C{-}NCH_3 \leftarrow & CO \quad CH.N(CH_3).CO \leftarrow & CO \quad CHNHCH_3 \\
| \quad \| & | \quad \quad \quad \; | & | \quad | \\
| \quad \; .CO & \quad \quad \quad NH_2 & | \quad | \\
CH_3N{-}C{-}NH & CH_3.N{-}CO & CH_3.N{-}CO
\end{array}
$$

$$
\begin{array}{ccc}
CH_3N{-}CO & & CH_3N{-}CO \\
| \quad | & & | \quad | \\
CO \quad C{-}NCH_3 & \rightarrow & CO \quad C{-}NCH_3 \\
| \quad \| & & | \quad \| \\
| \quad CCl & & | \quad C \\
CH_3N{-}C{-}N & & CH^3N{-}C{-}CH
\end{array}
$$
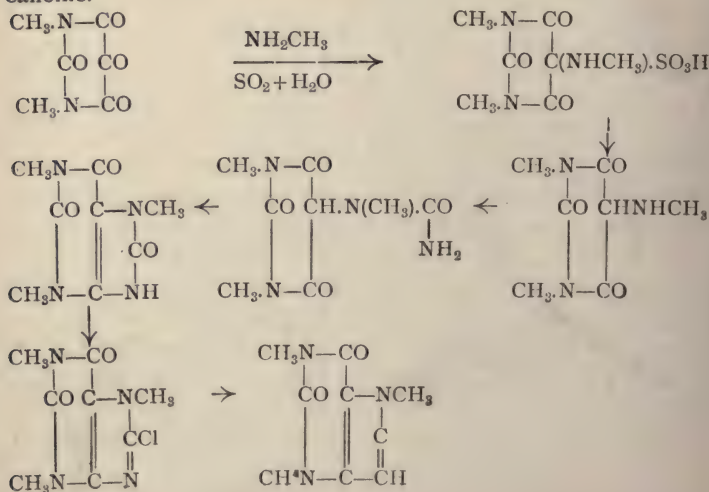
A year later saw yet another synthesis of caffeine, as follows. Hill's methyl uric acid, obtained by the action of methyl iodide on acid lead urate at 150° C., is 3-methyl uric acid, since Fischer showed that on treatment with phosphorus oxychloride and pentachloride it yielded 3-methyl-chloroxanthine. Further methylation of the latter substance in alkaline solution gave chloro-theobromine, and finally chloro-caffeine, from which caffeine is obtained by reduction.

$$
\begin{array}{ccc}
\text{NH.CO} & \text{NH.CO} & \text{NH.CO} \\
\text{CO C—NH} \rightarrow & \text{CO C—NH} \rightarrow & \text{CO C—NCH}_3 \\
\text{CO} & \text{C.Cl} & \text{C.Cl} \\
\text{CH}_3\text{N—C—NH} & \text{CH}_3\text{N—C—N} & \text{CH}_3\text{N—C—N} \\
\text{3-Methyl uric acid} & & \text{Chlorotheobromine}
\end{array}
$$

$$
\begin{array}{c}
\downarrow \\
\text{CH}_3\text{N—CO} \\
\text{CO C—NCH} \\
\text{CCl} \\
\text{CH}_3\text{N—C—N} \\
\text{Chlorocaffeine}
\end{array}
$$
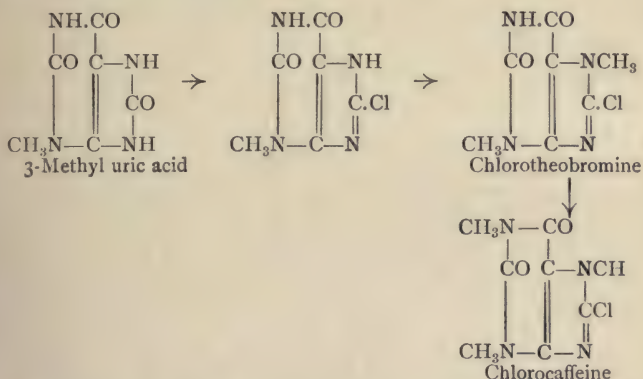
Somewhat recently Fischer and Ach have shown that caffeine may be transformed in paraxanthine, theophylline, and xanthine by preliminary treatment with phosphorus pentachloride. This leads to the formation of a small quantity of 7-methyl-2.6.8-tri-chloropurine and an amorphous compound. By slightly altering the experimental details the amphorous mass can be obtained as a 3^1-8-dichloro caffeine, which on hydrolysis by hydrochloric acid is converted into 8-chloro-paraxanthine. The latter on reduction yields paraxanthine.

$$
\begin{array}{ccc}
\text{CH}_3\text{N—CO} & \text{CH}_3\text{N—CO} & \text{CH}_3\text{N—CO} \\
\text{CO C—NCH}_3 \rightarrow & \text{CO C—NCH}_3 \rightarrow & \text{CO C—NCH} \\
\text{CH} & \text{CCl} & \text{CCl} \\
\text{CH}_3\text{N—C—N} & \text{Cl.CH}_2\text{.N—C—N} & \text{NH.C—N} \\
\text{Caffeine} & \text{3^1-8-dichlorocaffeine} & \text{8-chloroparaxanthine}
\end{array}
$$
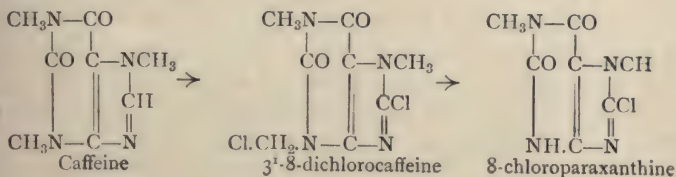
The same 3^1-8-dichlorocaffeine is obtained by chlorination at 160° C., but at 100° C., 7^1-8-dichloro caffeine results, and on hydrolysis yields 8-chlorotheophylline, which passes into theophylline by reduction. When caffeine is chlorinated at 160° C. by means of a solution of chlorine in phosphorus oxychloride, a tetrachloro caffeine ($1^1.3^1.7^1.8$) is formed, and on hydrolysis yields chloroxanthine. This, of course, passes into xanthine by reduction. In the hydrolysis of these compounds, the chlorinated methyl group is eliminated as formaldehyde and hydrochloric acid.

The synthetic production of xanthine was ultimately accomplished in a quite simple manner. It was found that treatment of 2.6.8-trichloro-purine with sodium ethoxide at ordinary temperature led to the replacement of the chlorine in position 6 by the ethoxyl group, but with excess of sodium ethoxide at 100° C. the two chlorine atoms at 2 and 6 were replaced by ethoxyl groups. The resulting compound was converted into xanthine by the action of hydriodic acid. Xanthine thus appears to be 2.6-dihydroxy-purine.
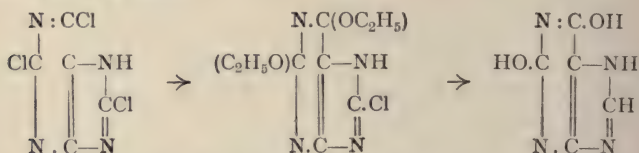
It is also formed, as Strecker had originally showed, by the action of nitrous acid on guanine (2-amino-6-hydroxy-purine).

The latter compound may be prepared from 2.6.8-trichloro-purine, which, by the action of caustic potash, is converted into 6-hydroxy-2.8-dichloro-purine. The chlorine atom in position 2 is replaced by the amino group when this substance is heated with alcoholic ammonia, and the resulting 2-amino-6-hydroxy-8-chloro-purine on reduction yields guanine.

A word might be said here as to a curious formation of 7-methyl guanine. This is obtained in a direct manner by the action of ammonia on 7-methyl-6-hydroxy-2-chloro-purine, itself formed by successive treatment of theobromine with phosphorus

oxychloride and caustic soda, the first product obtained being
7-methyl-2.6-dichloro-purine. If this compound be subjected to
the action of ammonia, 7-methyl-6-amino-2-chloro-purine results,
and by hydrolysis with caustic alkalies it would be expected that
a 7-methyl-6-amino-2-hydroxy-purine would be obtained, and
not the isomeric 7-methyl guanine. Since, however, 7-methyl
guanine is formed the explanation of the reaction seems to be in
the fission of the ring between positions 1 and 6, followed by
elimination of the elements of hydrochloric acid from the chlorine
in position 2 and the amino-group in position 6, with consequent
formation of the ring system again.

$$
\begin{array}{ccc}
\text{N:C.NH}_2 & \text{H}_2\text{NCO} & \text{NH.CO} \\
| \quad | & | & | \quad | \\
\text{Cl.C} \;\; \text{C—NCH}_3 & \text{H}_2\text{N.C.Cl} \;\; \text{C—NCH}_3 & \text{H}_2\text{NC} \;\; \text{C—NCH}_3 \\
\| \quad \| \quad \text{CH} \; \rightarrow & \| \quad \| \quad \text{CH} \; \rightarrow & \| \quad | \quad \text{CH} \\
\| \quad \| \quad \| & \| \quad \| & \| \quad \| \\
\text{N. C—N} & \text{N———C—N} & \text{N — C—N}
\end{array}
$$
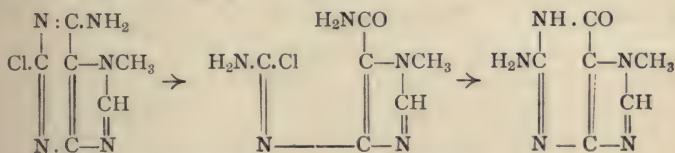
Three dimethyl-xanthines occur naturally, viz., the 1.7-
dimethyl-xanthine, or paraxanthine; the 1.3-dimethyl-xanthine
or theophylline, and the 3.7-dimethyl-xanthine or theobromine,
all of which have been synthesized. Paraxanthine is shown to
be the 1.7-dimethyl-xanthine in the following manner. 7-methyl-
2.6-dichloro-purine by successive treatment with alkali and
ammonia yields a 7-methylaminohydroxy-purine, which on oxida-
tion with chlorine yields guanidine, and consequently must
possess the structural formula (I), so that the 7-methyl-hydroxy-
chloro-purine must be (II). Now (II) on methylation gives a
dimethyl compound which can only possess the structure shown
in (III), and since this, on heating with hydrochloric acid, yields
paraxanthine, the methyl groups must consequently occupy
positions 1 and 7.

$$
\begin{array}{ccc}
\text{HN.CO} & \text{HN.CO} & \text{CH}_3\text{.N.CO} \\
| \quad | & | \quad | & | \quad | \\
\text{H}_2\text{N.C} \;\; \text{C.N.CH}_3 & \text{Cl.C} \;\; \text{C.N.CH}_3 & \text{Cl.C} \;\; \text{C.N.CH}_3 \\
\| \quad \| \quad \text{CH} & \| \quad \| \quad \text{CH} & \| \quad \| \quad \text{CH} \\
\| \quad \| \quad \| & \| \quad \| \quad \| & \| \quad \| \quad \| \\
\text{N. C. N} & \text{N. C. N} & \text{N. C. N} \\
\text{(I)} & \text{(II)} & \text{(III)} \quad \text{Chloropara-} \\
& & \text{xanthine}
\end{array}
$$
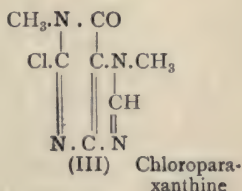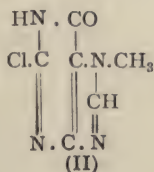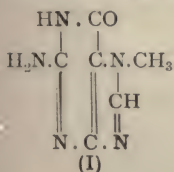
A second synthesis took as its starting-point 1.7-dimethyl uric acid prepared from monomethyl alloxan, methylamine, and sulphurous acid, the resulting 1.7-dimethyl uramil on treatment with potassium cyanate yielding the corresponding 1.7-dimethyl pseudo-uric acid, which on dehydration was converted into 1.7-dimethyl uric acid. This acid when heated with phosphorus oxychloride yields chloroparaxanthine, from which paraxanthine is obtained by reduction.

$$
\begin{array}{ccccc}
CH_3.N\!-\!CO & & CH_3.N\!-\!CO & & CH_3.N\!-\!CO \\
| \quad\quad | & & | \quad\quad | & & | \quad\quad | \\
CO \quad CO & \rightarrow & CO \quad C(NHCH_3).HSO_3 & \rightarrow & CO \quad CH.NH.CH_3 \\
| \quad\quad | & & | \quad\quad | & & | \\
HN\!-\!CO & & HN\!-\!CO & & HN.CO
\end{array}
$$

$$
\downarrow
$$

$$
\begin{array}{c}
CH_3.N\!-\!CO \\
| \quad\quad | \\
CO \quad CH.N.CH_3 \\
| \quad\quad | \\
HN\!-\!CO \quad CONH_2
\end{array}
$$

$$
\downarrow
$$

$$
\begin{array}{ccccc}
CH_3N\!-\!CO & & CH_3N\!-\!CO & & CH_3N\!-\!CO \\
| \quad\quad | & & | \quad\quad | & & | \quad\quad | \\
CO \quad C\!-\!NCH_3 & & CO \quad C\!-\!NCH_3 & & CO \quad C\!-\!NCH_3 \\
| \quad\quad \| & \prec & | \quad\quad \| & \leftarrow & | \quad\quad \| \\
| \quad\quad CH & & | \quad\quad CCl & & | \quad\quad CO \\
| \quad\quad \| & & | \quad\quad \| & & | \\
HN\!-\!C\!-\!N & & HN\!-\!C\!-\!N & & HN\!-\!C\!-\!NH
\end{array}
$$
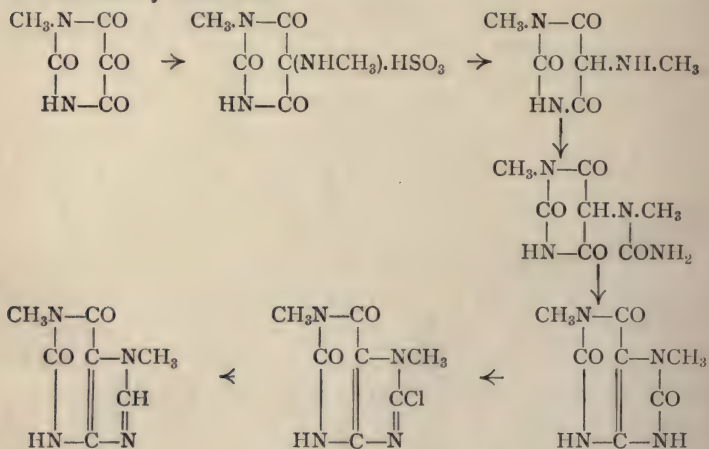
The synthetical preparation of theophylline has been given above (p. 114), while that of theobromine is carried out as follows. Alloxan, methylamine, and sulphurous acid may be condensed together to give methyl uramil as shown in the examples above, and from this 7-methyl uric acid may be obtained in the usual way. The lead salt of this acid is then methylated, and 3.7-dimethyl uric acid is formed, which on treatment with phosphorus oxychloride is converted into 3.7-dimethyl-6-chloro-2.8 dihydroxy-purine. By the action of ammonia on this substance the amino-group is introduced in position 6, and the hydroxyl group in position 8 is then replaced by chlorine through the agency of phosphorus oxychloride. Reduction of this chloro-compound gives 3.7-dimethyl-6-amino-2-hydroxy-purine, which by nitrous acid is converted into theobromine.

$$
\begin{array}{ccc}
\begin{matrix}
\text{HN—CO} \\
\text{CO C—NCH}_3 \\
\quad\ \text{CO} \\
\text{HN—C—NH}
\end{matrix}
&\rightarrow&
\begin{matrix}
\text{HN—CO} \\
\text{CO C—NCH}_3 \\
\quad\ \text{CO} \\
\text{CH}_3\text{N—C—NH}
\end{matrix}
&\rightarrow&
\begin{matrix}
\text{N}=\text{C.Cl} \\
\text{CO C—NCH}_3 \\
\quad\ \text{CO} \\
\text{CH}_3\text{N—C—NH}
\end{matrix}
\end{array}
$$

$$
\downarrow
$$

$$
\begin{matrix}
\text{N}=\text{C.NH}_2 \\
\text{CO C—NCH}_3 \\
\quad\ \text{CO} \\
\text{CH}_3\text{N—C—NH}
\end{matrix}
$$

$$
\begin{array}{ccc}
\begin{matrix}
\text{HN—CO} \\
\text{CO C—NCH}_3 \\
\quad\ \text{CH} \\
\text{CH}_3\text{N—C—N}
\end{matrix}
&\leftarrow&
\begin{matrix}
\text{N}=\text{C.NH}_2 \\
\text{CO C—NCH}_3 \\
\quad\ \text{CH} \\
\text{CH}_3\text{N—C—N}
\end{matrix}
&\leftarrow&
\begin{matrix}
\text{N}=\text{C.NH}_2 \\
\text{CO C—NCH}_3 \\
\quad\ \text{C.Cl} \\
\text{CH}_3\text{N—C—N}
\end{matrix}
\end{array}
$$
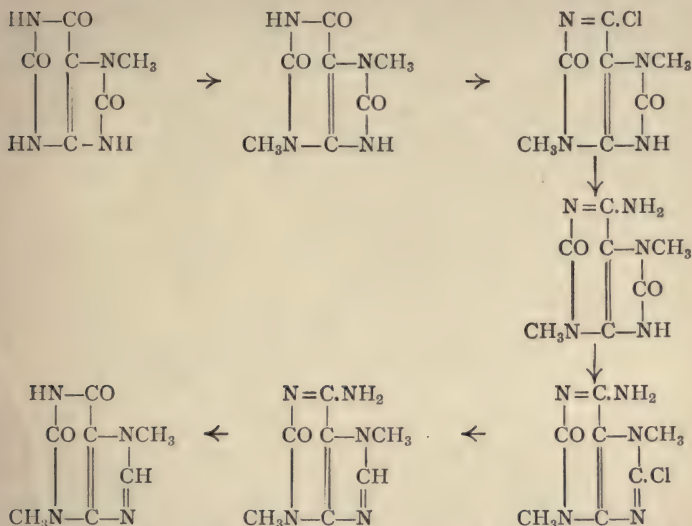
Of the other members of the series, the most important, perhaps, is sarcine (hypoxanthine) or 6-hydroxy-purine. This is obtained directly from 2.6.8-trichloro-purine, by heating it with a dilute solution of caustic potash when 6-hydroxy-2.8-dichloropurine or dichlorohypoxanthine is produced. Direct reduction converts this into sarcine. Another naturally occurring product, adenine (6-amino-purine), a decomposition product of nucleins, has also been obtained from 2.6.8-trichloropurine, which by the action of ammonia is converted into 6-amino-2.8-dichloropurine, reduction of this latter compound furnishing adenine.

Numerous other derivatives of the previously mentioned compounds have also been synthesized by Fischer and his pupils, for the details of which the original papers should be consulted, a complete summary containing references to the earlier papers appearing in the *Berichte*, 1899, 32, p. 435.

Thus the vexed question of the constitution of uric acid and its related compounds was solved, and apparently little more work appeared to be required in connection with these compounds when, in 1900, Traube published a complete new series

of synthetical preparations of the chief members of the group. The first paper issued, dealt only with the formation of guanine, the starting-point for which was the condensation of guanidine with cyanacetic ester, the resulting cyanacetyl guanidine on treatment with caustic soda solution undergoing ring closing, with formation of 2.4.-diamino-6-hydroxy pyrimidine.

$$
\begin{array}{ccc}
\mathrm{NH_2} & \mathrm{ROOC} \\
\mathrm{HN{:}C} & + & \mathrm{CH_2} \\
\mathrm{NH_2} & \mathrm{CN}
\end{array}
\rightarrow
\begin{array}{c}
\mathrm{HN-CO} \\
\mathrm{HN{:}C \quad CH_2} \\
\mathrm{NH_2 \ CN}
\end{array}
\rightarrow
\begin{array}{c}
1 \quad \mathrm{HN-CO} \quad 6 \\
2 \ \mathrm{HN:C \quad CH_2} \ 5 \\
3 \quad \mathrm{HN-C{:}NH} \ 4 \\
\text{or} \\
\mathrm{N-C.OH} \\
\mathrm{H_2N.C \quad CH} \\
\mathrm{N-C.NH_2}
\end{array}
$$
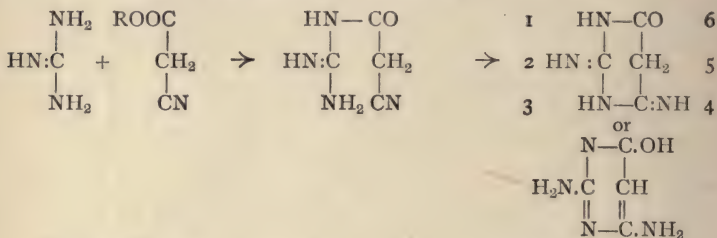
This base readily forms an isonitroso-derivative which, on reduction by ammonium sulphide, passes into 2.4.5-triamino-6-hydroxypyrimidine, and this latter on boiling with formic acid is converted into guanine, a reaction resembling the formation of the anhydro-bases, which are obtained when an orthodiamine is heated with a fatty acid.

$$
\begin{array}{c}
\mathrm{HN-CO} \\
\mathrm{HN{:}C \quad CH.NH_2} \\
\mathrm{HN-C{:}NH}
\end{array}
\text{ or }
\begin{array}{c}
\mathrm{N=C.OH} \\
\mathrm{H_2N.C \quad C.NH_2} \\
\mathrm{N-C.NH_2}
\end{array}
\xrightarrow{\mathrm{HCOOH}}
$$

$$
\mathrm{2\,H_2O} +
\begin{array}{c}
\mathrm{HN.CO} \\
\mathrm{H_2NC \quad C-NH} \\
\mathrm{\quad\quad CH} \\
\mathrm{N.C-N}
\end{array}
$$
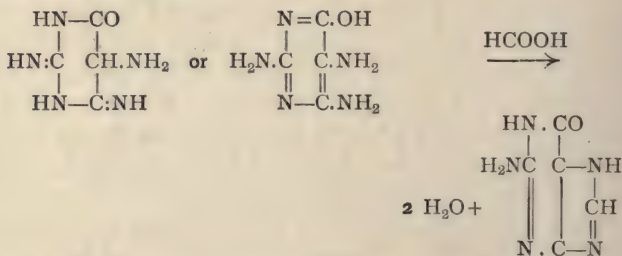
In the second paper in the same year the synthesis of uric acid, xanthine, theobromine, theophylline, and caffeine were described, the method employed being, in the first stages, substantially that given above. The starting-point in these preparations was cyanacetyl urea, which was formed by the condensation of urea and cyanacetic ester in the presence of phosphorus oxychloride. This urea derivative passes into the isomeric 4-amino-2.6-

dihydroxy pyrimidine on treatment with a forty per cent. solution of caustic soda, and from this by conversion into the isonitroso-compound and subsequent reduction with ammonium sulphide, 4.5-diamino-2.6-dihydroxypyrimidine is obtained. For the preparation of uric acid the sulphate of the base is dissolved in an excess of dilute caustic soda solution, and chlorocarbonic ester is added, the resulting urethane derivative on heating to 180-190° C. passing into uric acid by loss of the elements of alcohol.
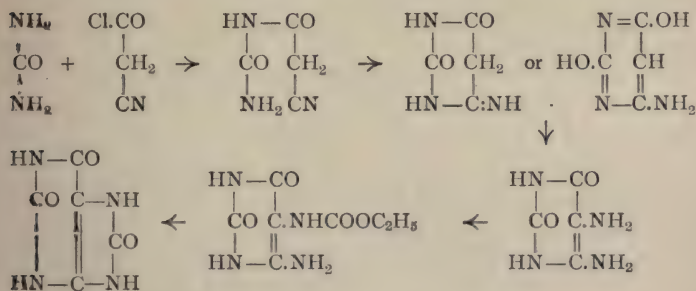
If xanthine be required, the diamino-hydroxy-pyrimidine is converted into its formyl derivative, the sodium salt of which on heating to 220° C. loses one molecule of water and passes into sodium xanthine.
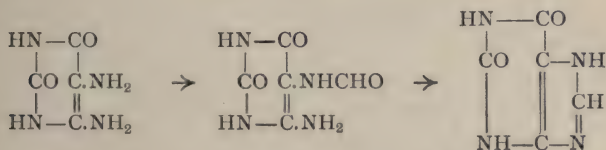
Theophylline is obtained in a precisely similar manner, starting out from symmetrical dimethyl urea and cyanacetyl chloride, the scheme of operations being identical with that used in the synthesis of xanthine. For the preparation of caffeine the method is again similar as far as the formation of the formyl derivative of 1.3-dimethyl-4.5-diamino-2.6-dioxypyrimidine, and here an

ingenious method is used for introducing the third methyl group. The group $\diagup$C.NH.CHO on, heating with an alcoholic solution of sodium ethoxide, passes into $\diagup$C.N.Na.CHO, and this resulting sodium salt when heated with methyl iodide yields caffeine.

```
CH₃.N — CO                    CH₃N — CO
      |      |                       |      |
      CO  C.NHCHO    →          CO  C – N(Na)CHO
      |      ‖                       |      ‖
CH₃.N — C.NH₂                 CH₃N — C.NH₂
                                        ↓
CH₃N — CO                     CH₃N — CO
      |     |                         |     |
      CO  C — NCH₃                 CO  C – N(CH₃)CHO
      |     ‖  |                      |     ‖
      |     |  CH          ←          |     |
      |     |  ‖                      |     |
CH₃N — C — N                  CH₃N — C.NH₂
```
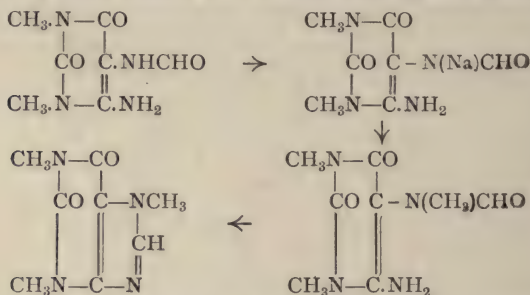
Theobromine is prepared in a similar way from 3-methyl-4.5-diamino-2.6-dioxypyrimidine, the starting out materials for which are monomethyl urea and cyanacetyl chloride. The formyl derivative of the pyrimidine, on heating to 220° C., is transformed into 3-methyl xanthine, methylation of which in slightly alkaline solution, at 80° C., yields theobromine—

```
HN — CO            HN — CO            HN — CO
    |    |              |    |              |    |
    CO  C.NHCHO         CO  C.NH            CO  C.N.CH₃
    |    ‖              |    |  |           |    |  |
    |    |        →     |    |  CH    →     |    |  CH
    |    |              |    |  ‖           |    |  ‖
CH₃.N — C.NH₂      CH₃.N — C.N        CH₃.N — C.N
```
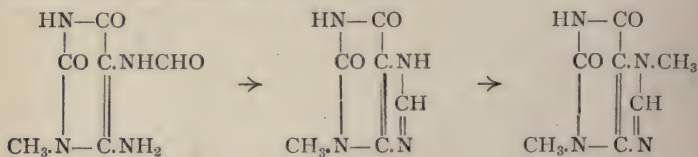
As a further contribution to the synthetical preparations in the group, Oskar Isay has recently (1906) shown how various purine derivatives may be obtained from nitro-uracils. 5-nitrouracil, on treatment with phosphorus oxychloride, is converted into 2.4-dichloro-5-nitropyrimidine, which, in contact with *cold* ammonia, passes into 2-chloro-4-amino-5-nitropyrimidine, and from this by reduction 4.5-diamino pyrimidine is obtained. This base when heated with formic acid yields purine itself: if acetic acid be employed an 8-methyl purine results, and if it be heated with urea, 8-oxypurine is formed.

$$
\begin{array}{c}
\text{HN—CH} \\
| \quad \| \\
\text{CO} \quad \text{C.NO}_2 \\
| \quad \quad | \\
\text{HN—CO}
\end{array}
\quad \text{or} \quad
\begin{array}{c}
\text{N : CH} \\
| \quad \quad | \\
\text{HO.C} \quad \text{C.NO}_2 \\
\| \quad \quad \| \\
\text{N.C.OH}
\end{array}
\xrightarrow{\text{POCl}_3}
\begin{array}{c}
\text{N : CH} \\
| \quad \quad | \\
\text{Cl.C} \quad \text{C.NO}_2 \\
\| \quad \quad \| \\
\text{N.C.Cl}
\end{array}
\xrightarrow{\text{NH}_3}
\begin{array}{c}
\text{N : CH} \\
| \quad \quad \| \\
\text{Cl.C} \quad \text{C.NO}_2 \\
\| \quad \quad \| \\
\text{N.C.NH}_2
\end{array}
$$

$$
\begin{array}{c}
\text{N:CH} \\
| \quad \quad | \\
\text{HC} \quad \text{C.NH} \\
\quad \quad | \\
\quad \text{CH} \\
\| \quad \quad \| \\
\text{N.C.N}
\end{array}
\xleftarrow{\text{HCOOH}}
\begin{array}{c}
\text{N:CH} \\
| \quad \quad | \\
\text{HC} \quad \text{C.NH}_2 \\
\| \quad \quad \| \\
\text{N.C.NH}_2
\end{array}
\xrightarrow{\text{Urea}}
\begin{array}{c}
\text{N.CH} \\
| \quad \quad | \\
\text{HC} \quad \text{C—NH} \\
\quad \quad \quad | \\
\quad \quad \text{CO} \\
\| \quad \quad | \\
\text{N.C—NH}
\end{array}
$$
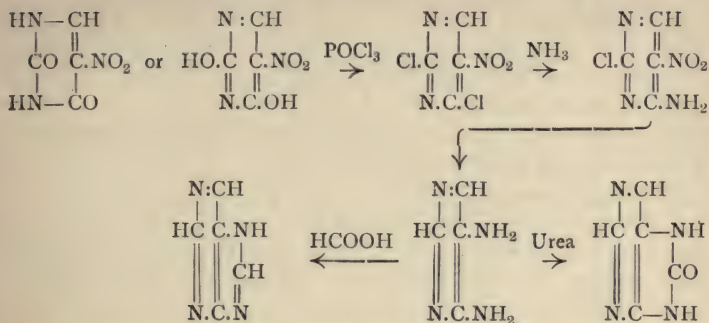
If, however, the dichloro-nitropyrimidine be brought into contact with warm ammonia, both the chlorine atoms are replaced by amino groups, and the diamino-nitropyrimidine may then be reduced to a triamino-pyrimidine, which readily condenses with formic acid to yield 2-amino purine or iso-adenine.

$$
\begin{array}{c}
\text{N:CH} \\
| \quad \quad | \\
\text{H}_2\text{N.C} \quad \text{C.NO}_2 \\
\| \quad \quad \| \\
\text{N.C.NH}_2
\end{array}
\xrightarrow{\text{H}}
\begin{array}{c}
\text{N:CH} \\
| \quad \quad | \\
\text{H}_2\text{N.C} \quad \text{C.NH}_2 \\
\| \quad \quad \| \\
\text{N.C.NH}_2
\end{array}
\xrightarrow{\text{HCOOH}}
\begin{array}{c}
\text{N:CH} \\
| \quad \quad | \\
\text{H}_2\text{N.C} \quad \text{C.NH} \\
\quad \quad \quad | \\
\quad \quad \text{CH} \\
\| \quad \quad \| \\
\text{N.C.N}
\end{array}
$$
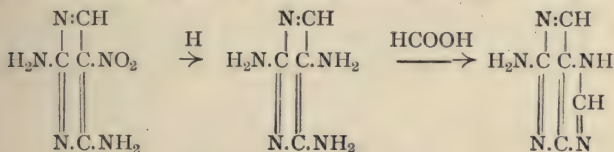
The electrolytic reduction of purine derivatives has been studied by Tafel and his pupils, who find that if the reduction be carried out in sulphuric acid solution, xanthine and its homologues unite with four atoms of hydrogen, eliminating water and yielding desoxy-compounds of basic character ; thus from 3-methyl xanthine, 3-methyl desoxyxanthine is obtained.

$$
\begin{array}{c}
\text{HN—CO} \\
| \quad \quad | \\
\text{CO} \quad \text{C—NH} \\
| \quad \quad \| \quad | \\
\quad \quad \quad \text{CH} \\
| \quad \quad \| \\
\text{CH}_3\text{N—C—N}
\end{array}
\xrightarrow{\text{H}}
\text{H}_2\text{O} +
\begin{array}{c}
\text{HN—CH}_2 \\
| \quad \quad | \\
\text{CO} \quad \text{C—NH} \\
| \quad \quad | \\
\quad \quad \quad \text{CH} \\
| \quad \quad \| \\
\text{CH}_3\text{N—C—N}
\end{array}
$$
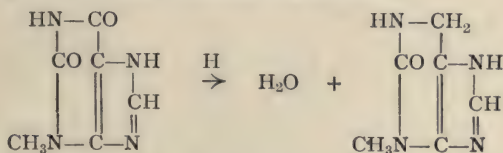
Uric acid, however, requires six atoms of hydrogen per molecule of acid, and gives purone, $C_5H_8N_2O_4$, as a product ; and it was shown that it must be the $>CO$ group in position 6 which has

been reduced to a $> CH_2$ group with simultaneous addition of a hydrogen atom at 4 and 5, because on hydrolysis with caustic baryta one molecule of purone gives rise to two molecules of urea in the form of its decomposition products, carbon dioxide and ammonia, which can only be the case if the $>CO$ groups in positions 2 and 8 are unattacked.

It is found necessary in the above reduction processes to employ cathodes of very pure lead (those actually used not containing more than 0.015 per cent. of foreign metals) since impurities in the electrodes diminish the yield of reduction product, the cause being that hydrogen is only evolved by the passage of the electric current through sulphuric acid when the potential difference between the electrodes reaches a certain value. This value is a minimum for platinum electrodes, but is much greater for lead electrodes, that is, a supertension is necessary before the hydrogen is evolved when lead electrodes are used, and as the difference of potential affects the energy with which the discharged ions can react, it is found that reduction processes which cannot be carried out by other methods are possible where such a supertension exists.

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CHAPTER IV

THE ALKALOIDS

THE term alkaloid, in its widest sense, was first applied to all nitrogenous basic compounds present in plants, or which were derived from plant tissues by various extraction operations, and thus such diverse substances as methylamine, asparagine, caffeine, morphine, etc., were included in the one main group. But with the development of synthetic organic chemistry a more restricted use of the term was adopted, and in 1880 Königs suggested that it should be reserved for those particular members which were derived from pyridine. However, with the increasing knowledge of the constitution of these substances, which has been largely extended in recent years, it has been shown that Königs' classification is not comprehensive enough, and the term is now more generally extended to include those nitrogenous basic constituents of plants which may be considered as derived from pyridine, quinoline, and isoquinoline, together with those of unknown constitution.

The alkaloids are found widely distributed in the vegetable kingdom, practically all being found in dicotyledonous plants, many being found to a large extent in certain particular plant families, such as the Solanaceæ and Papaveraceæ, whilst other families, such as the Labiateæ and Rosaceæ, have not as yet been found to contain any alkaloids. They do not as a rule exist in the free state, but are generally found as salts of various organic acids, such, for example, as malic acid, citric acid, tannic acid, quinic acid (which usually accompanies the cinchona alkaloids), meconic acid (usually found with the opium alkaloids), and aconitic acid. Most alkaloids are solids containing carbon, hydrogen, nitrogen, and oxygen, and are crystalline and non-volatile; coniine, nicotine, and sparteine, on the other hand,

contain carbon, hydrogen, and nitrogen only, and are volatile liquids. Almost all are optically active and lævo-rotatory. They have an alkaline reaction in the majority of cases, and a bitter taste. Most alkaloids are insoluble, or only very slightly soluble, in water, but are readily soluble in alcohol, and less readily in ether and chloroform. Primary bases have not been met with among the alkaloids (using the term in its restricted sense) and only a few secondary bases are known (the most important being coniine). The majority are tertiary bases, the nitrogen atom being bound very tightly in the molecule, since it forms part of a ring system and is not a constituent of an open chain. The only amines yet obtained in the decomposition of alkaloids are the methylamines, so that apparently the methyl group is the only alkyl group which is known to be attached to the nitrogen atom in various alkaloids.

Some substances precipitate many of the alkaloids from their aqueous or acid solutions, the more important of such general alkaloid reagents being

Sonnenschein's reagent (sodium phosphomolybdate), which in the presence of nitric acid gives a yellowish-white flocculent precipitate, from which the alkaloid may be recovered by heating with barium carbonate and water. Scheibler recommends phosphotungstic acid similarly.

Mayer's solution of potassium mercuric iodide, which gives yellowish-white precipitates with most alkaloids, the precipitates being insoluble in acids and in dilute alkalies. The alkaloid may be recovered from the precipitate by digestion with stannous chloride and caustic soda.

Potassium bismuthous iodide, which gives precipitates of the general type $3NR_4I.2BiI_3$, and is generally used in the presence of dilute sulphuric acid or of hydriodic acid.

Picric acid precipitates many. *Iodine* (in potassium iodide solution) in some cases gives brown precipitates of periodides, preferably in acid solution. *Tannic acid* precipitates most alkaloids. The chlorides of gold and platinum also yield precipitates with the alkaloids.

In extracting alkaloids from plants, these are lixiviated by

means of acidified water in a percolator, the solution rendered alkaline, and volatile alkaloids distilled over in a current of steam. The fixed alkaloids which are precipitated on the addition of alkali can be extracted from other substances present by the use of various solvents. Or the infusion of the alkaloid may be treated successively with lead acetate, basic lead acetate, and ammonia, the excess of lead removed by sulphuretted hydrogen, and the alkaloid precipitated by one of the special reagents mentioned above. The free base may then be recovered by a suitable decomposition of the precipitate so obtained.

The alkaloids considered in the following pages may be approximately classified as follows :—

Pyridine derivatives :—Arecaidine, trigonelline, piperine, coni-
   ine, nicotine.
Quinoline derivatives :—Strychnine, brucine, cinchonine, and
   quinine.
Isoquinoline derivatives :—Berberine, hydrastine, laudanosine,
   narcotine, papaverine, codeine, morphine, thebaine, and
   corydaline.
Pyrrolidine derivatives :—Atropine, cocaine.

In investigations on the constitution of the alkaloids, certain main principles are usually followed out ; thus hydroxylic groups are recognized by conversion into acetyl or benzoyl derivatives, and if in addition the group be phenolic, it is shown by the fact that the compound in question is readily soluble in caustic alkali, and will also yield alkyl ethers.

Methoxyl groups are readily recognized by the Zeisel reaction, in which the substance is heated with fuming hydriodic acid to about 140° C., and the methyl group is eliminated as methyl iodide.

Oxygen again, in the form of a carboxyl group, may be identified by the readiness with which the compound will esterify, and if present as an ester may be detected by hydrolysis of the parent substance into acid and alcohol. The determination of the conditions under which nitrogen is present in the molecule is, as a rule, a matter of more difficulty, distillation with caustic

alkali yielding in some cases the various methylamines, and so pointing to the presence of nitrogen combined with one or more methyl groups. A more elaborate process consists in the exhaustive methylation process of Hofmann, by which the compound is converted into the hydroxide of a quaternary base and then heated alone or with caustic alkali, when the nitrogen is eliminated as a tertiary amine and an unsaturated hydrocarbon is formed, from which it is often possible to arrive at some ideas as to the structure of the original base (see coniine). Oxidation methods are also frequently used, and lead to the formation of substances of simpler nature from which ideas of structure are obtained. Distillation over zinc dust has been resorted to in some cases, and has led to the formation of pyridine and its homologues, but such drastic reactions as this are, as a rule, not of much use as aids to the determination of structure, since they lead to deepseated changes which cannot be successfully traced back, in the majority of instances.

Pyridine Group.—*Arecaidine*, $C_7H_{11}O_2N$, was first isolated in 1888-1891 by Jahns from the betel-nut, in which it occurs in combination chiefly with tannic acid, three other alkaloids, namely, arecaine, $C_7H_{11}O_2N$, guvacine, $C_6H_9O_2N$, and arecoline, $C_8H_{13}O_2N$, being also present in the nuts. It crystallizes in plates which contain one molecule of water of crystallization, and in the anhydrous state melts at 223° C. It possesses an acidic character, since it may be esterified, a fact pointing to the presence of the carboxyl group. It is also of a basic character. The nitrogen atom is attached directly to a methyl group, since when heated with caustic baryta or with lime, methylamine is eliminated, the presence of such a methyl group being also demonstrated by the fact that when the alkaloid is heated under pressure with hydrochloric acid, methyl chloride is obtained. Again, on reduction, the alkaloid combines with two atoms of hydrogen and forms a dihydro-arecaidine, which shows that the grouping $C = C$ exists in the molecule, and thus in all probability it may be considered as

$$HOOC.C_5H_7 : N.CH_3,$$
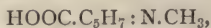
that is, as the carboxylic acid of a methyl piperideïne, a result

confirmed by the fact that both arecaidine and dihydro-arecaidine are obtained when the methyl chloride of nicotinic acid is reduced by tin and hydrochloric acid.

$$HOOC.C_5H_4N(CH_3).Cl + 4H = HOOC.C_5H_7 : NCH_3 + HCl$$
$$HOOC.C_5H_4N(CH_3).Cl + 6H = HOOC.C_5H_9 : NCH_3 + HCl$$
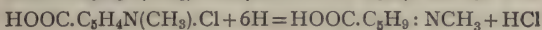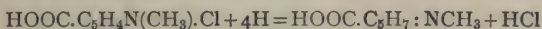
The structure of the alkaloid was definitely settled in 1908 by Wöhl, who prepared it synthetically by the following method. The acetal of β-chloropropionic aldehyde, on condensation with methylamine, yields a tertiary base which, under the action of cold hydrochloric acid passes into the aldehyde of a methyl piperideïne carboxylic acid. The aldehyde is then converted into its oxime, and the oxime into the nitrile by dehydration, hydrolysis of the nitrile giving rise to the carboxylic acid, identical with arecaidine.

$$CH_3NH_2 + 2Cl.CH_2.CH_2.CH(OR)_2 \longrightarrow CH_3N[CH_2.CH_2.CH(OR)_2]$$
$$\downarrow HCl$$
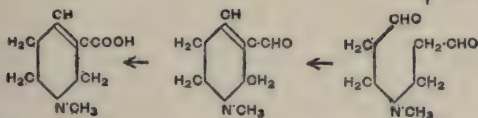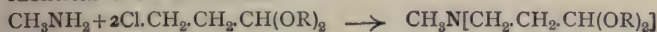
Trigonelline, $C_7H_7O_2N$, was also first isolated by Jahns in 1885 from the seeds of *Trigonella*, and has since been recognized as occurring in flax, in oats, and in the seeds of *Strophantus hispidus* and *S. Kombé*, where it is found associated with strophanthin and choline. Trigonelline is readily soluble in water. When heated with baryta water it yields methylamine, a reaction showing that the group $-N.CH_3$ is present in the molecule, and again, when subjected to the action of hydrochloric acid at 260° C., it is converted into methyl chloride and nicotinic acid ; these reactions being identical with those of the methyl betaine of nicotinic acid, which was prepared by Hantzsch before Jahns had isolated trigonelline. Thus the alkaloid possesses the following constitution :—

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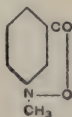
further confirmation of which was given by Pictet and Genequand in 1897, who found that when nicotine iso-methiodide was converted into the hydroxide, and the latter oxidized by potassium permanganate in aqueous solution, it was immediately converted into the methyl betaine of nicotinic acid, identical in every respect with trigonelline.
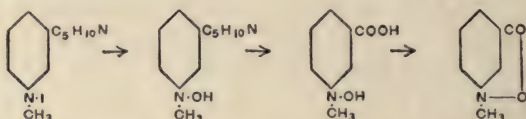
Piperine, $C_{17}H_{19}O_3N$, is found in the fruits of *Piper nigrum* and *Piper longum*. It crystallizes in prisms, is inactive, and melts at 129° C. Practically the first step taken to elucidate the constitution of this alkaloid was that due to von Babo and Keller, who showed that on hydrolysis with alcoholic potash it gave piperidine (hexahydropyridine) and piperic acid.

$$C_{17}H_{19}O_3N + KOH = C_5H_{11}N + C_{12}H_9O_4K.$$
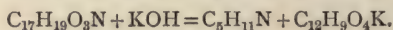
Hence one has in piperine the grouping
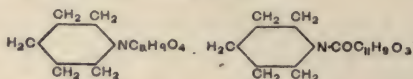
and since the constitution of piperidine is known (from its relation to pyridine), it only remains to determine that of piperic acid. This acid, on oxidation with potassium permanganate, yields piperonal, $C_7H_5O_2.CHO$, and piperonylic acid, $C_7H_5O_2.COOH$. It is also an unsaturated acid, since it readily takes up four atoms of bromine, and on reduction combines with four atoms of hydrogen. Piperonylic acid, on the other hand, is a saturated monobasic acid, which, when heated with water under pressure to about 200° C., is decomposed into protocatechuic acid, $C_7H_6O_4$, and carbon.

$$C_7H_5O_2.COOH = C + C_6H_5O_2.COOH$$
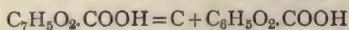
This reaction points to piperonylic acid as being a derivative of protocatechuic acid, confirmation of which fact was given when

Fittig and Remsen synthesized it by the action of methylene iodide upon protocatechuic acid in the presence of potassium hydroxide,
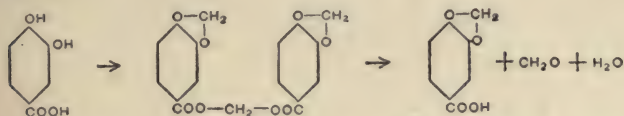
and thus piperonylic acid appears as the methylene ether of protocatechuic acid. Now, since piperonylic acid possesses the empirical formula $C_7H_5O_2.COOH$, and piperic acid is $C_{11}H_9O_2.COOH$, the difference between the two compounds in question is that of a group C_4H_4, and this must of necessity lie between the phenyl group in the piperonylic acid and the carboxyl group, for were it in any other position it would mean that another side chain would be present in the piperic acid molecule, and, consequently, on oxidation piperic acid would yield at least a dibasic acid, whereas only the monobasic piperonylic acid is formed. Hence piperic acid must possess the following constitution :—
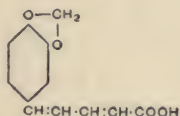
This constitutional formula has received further confirmation from two different sources, firstly, from Dœbner's observation that the acid, on oxidation by potassium permanganate, yields piperonal and racemic acid,
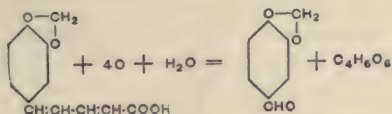
and, secondly, by the synthesis of piperic acid from piperonal by Ladenburg and Scholtz as follows. Piperonal in the presence of caustic alkalies condenses directly with acetaldehyde, water being eliminated from the reacting components and the un-

saturated piperonylacrolein being formed. This aldehyde, on heating with fused sodium acetate and acetic anhydride, behaves like benzaldehyde, that is, it undergoes the Perkin reaction, and the resulting substance obtained is the sodium salt of piperic acid

Piperonal   Piperonyl acrolein   Sodium piperate
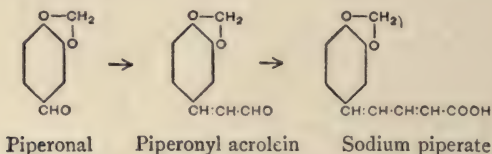
Thus, knowing the constitution of the products of fission of piperine, which are evidently produced by a reaction similar to that by which acetanilide is decomposed into acetic acid and aniline, it would seem most probable that piperine should be represented as
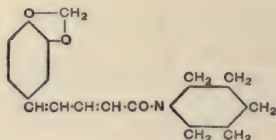
a result which is further confirmed by Rugheimers' synthesis of the alkaloid from piperidine and the chloride of piperic acid.

Coniine, $C_8H_{17}N$, is found, together with γ-coniceine, $C_8H_{15}N$, and conhydrine, $C_8H_{17}ON$, in the hemlock. It is one of the few alkaloids which are liquids. It is a colourless oil, boiling at 166° C., and in solution is dextro-rotatory. It behaves as a secondary base. The first ideas as to the constitution of this substance are due to the researches of Hofmann, who showed that when the alkaloid is distilled over zinc chloride, a basic compound of formula $C_8H_{11}N$ (*conyrine*) is produced, together with hydrogen. Now, since the oxidation of conyrine yields picolinic acid, a monobasic acid of the following structure :—

it follows that conyrine must be a pyridine derivative containing *one* side chain in the α-position, and it is consequently to be regarded as an α-propyl pyridine, $C_5H_4N(C_3H_7)$. The propyl group is the *normal* propyl group, because in the first place α-isopropyl pyridine, which is obtained on heating pyridine and isopropyl iodide to 290° C., is not identical with conyrine, and, secondly, on reduction with fuming hydriodic acid at high temperature, conyrine is converted into normal octane (and ammonia), a result that would not be obtainable if the isopropyl group were present.

$$HC:HC.C.CH_2.CH_2.CH_3 \atop HC:HC.N \overset{||}{} \quad + 10H \rightarrow NH_3 + \begin{matrix} CH_2.CH_2.CH_2.CH_2.CH_2.CH_3 \\ | \\ CH_2.CH_3 \end{matrix}$$
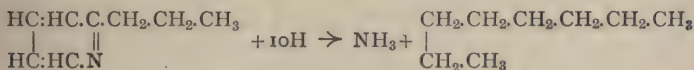
Since conyrine, $C_8H_{11}N$, and coniine, $C_8H_{17}N$, differ by a matter of six hydrogen atoms, it therefore appears to be probable that coniine is a hexahydro-conyrine, that is, a hexahydro-α-propyl pyridine or α-propyl piperidine, a fact confirmed by the synthesis of the alkaloid by Ladenburg from α-picoline as follows. Paraldehyde, when heated with α-picoline to high temperature, is partially converted into α-allyl pyridine, the reduction of the latter with sodium and alcohol yielding α-propyl piperidine.

α-picoline   α-allyl pyridine   α-propyl piperidine
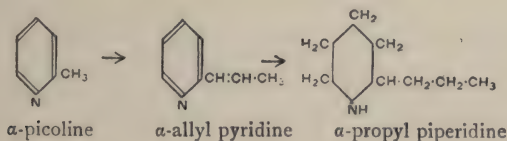
The base so formed resembles natural coniine in all respects except that it is optically inactive, whereas the natural base is dextro-rotatory. The artificial coniine is a racemic mixture, and may be split into its active components by fractional crystallization of the bitartrate of the base, but it is only quite recently that Ladenburg has succeeded in getting the rotation of the synthetic *d*-form to agree with that of the natural *d*-coniine, it being necessary to heat the synthetic product for many hours at 290° C. in order to get pure *d*-coniine.

Coniine possesses a certain amount of historical importance, as it was the first alkaloid prepared synthetically. Numerous decomposition products of coniine have been obtained at different times in the hope of elucidating its structure, and of these, perhaps, the most important is the hydrocarbon *conylene*, C_8H_{14}, which was first obtained by Wertheim on heating nitroso-coniine, $C_8H_{16}N.NO$, with phosphoric anhydride. It is also a product of the decomposition of the alkaloid in the destructive methylation process. The alkaloid, on treatment with methyl iodide, yields the methiodide of methyl coniine, from which, by the action of moist silver oxide, the corresponding hydroxide is obtained. On distillation of this hydroxide, the ring system is broken, water is eliminated, and the so-called *dimethylconiine* is formed. This tertiary base readily forms an ammonium salt by direct union with methyl iodide, the hydroxide of which (obtained as before by the action of moist silver oxide on the iodide) on distillation, decomposes, with elimination of the nitrogen atom, as tri-methylamine, and the formation of the hydrocarbon conylene.

$$C_8H_{16}{:}NH \xrightarrow{CH_3I} C_8H_{16}{:}N(CH_3)_2I \xrightarrow{Moist\ Ag_2O} C_8H_{16}{:}N(CH_3)_2.OH$$

$$\downarrow Heat$$

$$C_8H_{15}{:}N(CH_3)_3OH \longleftarrow C_8H_{15}{:}N(CH_3)_3I \xleftarrow{CH_3I} C_8H_{15}{:}N(CH_3)_2$$

$$\downarrow$$

$$N(CH_3)_3 + H_2O + C_8H_{14} \text{ or } C_3H_7CH{:}CH.CH_2.CH{:}CH_2$$
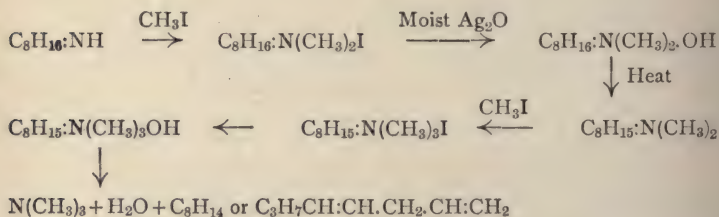
Various oxidation products may be obtained from coniine by working under different conditions, thus with strong oxidizing agents, such as chromic acid, nitric acid, etc., ammonia and normal butyric acid are produced, whilst Wolffenstein, by the action of hydrogen peroxide (in $3°/_0$ solution), obtained propyl-δ-aminovalerylaldehyde, $H_2N.CH(C_3H_7).CH_2.CH_2.CH_2.CHO$, a coniceine, $C_8H_{15}N$, and butyryl butyric acid, $C_3H_7.CO.CH_2.CH_2 CH_2.COOH$. Possibly too much faith must not be placed on these reactions, since by a similar oxidation of piperidine (of which

coniine is only a *n*-propyl derivative) Wolffenstein obtained what he at first considered to be a δ-aminovalerylaldehyde, $H_2N.CH_2.CH_2.CH_2.CH_2.CHO$, a view which he modified some few years later, the supposed aldehyde agreeing more nearly with the properties of a piperidinium oxide or oxime.
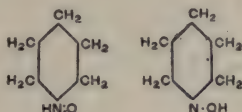
Other oxidation products have been obtained by Schotten and Baum, the nitrogen atom in the ring being first protected by converting the coniine into its benzoyl derivative; or into a urethane (by the action of chloro-carbonic ester), the ring system then on oxidation, in the first case by the action of nitric acid, and in the second case by potassium permanganate, being broken between the nitrogen atom and a neighbouring carbon atom, and yielding open chain compounds.

$$\downarrow HNO_3 \qquad\qquad \downarrow KMnO_4$$

$$ROOC.CH(C_3H_7)(CH_2)_2.COOR \qquad C_6H_5CO.NH.CH(C_3H_7)(CH_2)_3.COOH$$
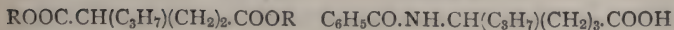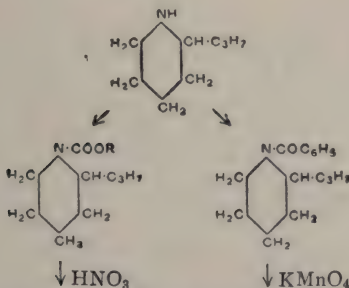
Nicotine, $C_{10}H_{14}N_2$.—Previous to 1901 it was supposed that nicotine was the only alkaloid existing in the leaves of the tobacco plant, but in that year Pictet and Rotschy showed that three other alkaloids, namely, nicotimine, $C_{10}H_{14}N_2$, nicoteine, $C_{10}H_{12}N_2$, and nicotelline, $C_{10}H_8N_2$, were also present,

only in relatively small quantities, since on working up 10 kilos of tobacco extract the authors obtained about 1 kilo of nicotine, 20 grams of nicoteine, 5 grams of nicotimine, and 1 gram of nicotelline.

Nicotine may be separated from the other members of the group by distillation of its aqueous alkaline solution in a current of steam. It is, when freshly prepared, a colourless oil of characteristic odour, boiling at 245°C. It behaves as an unsaturated di-acid base. The free alkaloid is strongly lævo-rotatory, its salts, however, are dextro-rotatory. It is a very active poison. On oxidation it yields nicotinic acid, $C_5H_4N.COOH$ (pyridine-β-carboxylic acid), and is thus in all probability to be considered as a pyridine derivative containing the complex $-C_5H_{10}N$ in the β-position.

One of the earliest structural formulæ given to nicotine was that of Etard, namely,
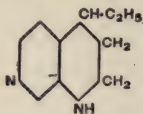
which, however, must be ruled out as inadmissible since such a compound could not, under any circumstances, be oxidized to nicotinic acid. Skraup and Vortmann then assumed the possibility of a dipyridyl structure for nicotine, and tried to synthesize the alkaloid as follows. By condensation of meta-phenylene diamine with glycerine and an oxidizing agent, phenanthroline is formed, which, on oxidation yields $\alpha\beta$-dipyridyl dicarboxylic acid. This acid on elimination of carbon dioxide from the carboxyl groups is converted into $\alpha\beta$-dipyridyl, para-phenylene diamine by the same treatment yielding $\beta\beta$-dipyridyl. The $\beta\beta$-derivative was then reduced in the hope of obtaining nicotine, but the compound obtained $C_{10}H_{14}N_2$ (pyridylpiperidine) was not identical with the alkaloid.

ψ-phenanthroline

phenanthroline

ββ-dipyridyl

αβ-dipyridyl

$C_{10}H_{14}N_2$
nicotidine

$C_{10}H_{14}N_2$
dipiperidyl
(not identical with
hexahydro-nicotine)
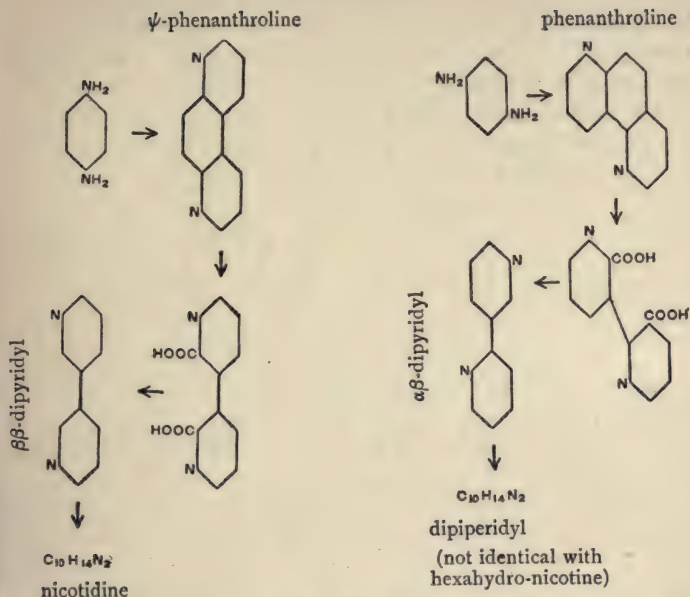
Thus it seems apparent that the ring system attached to the pyridine nucleus is not a six-membered system, and Pinner assumed the possibility of a five-membered ring being present, and assigned to the alkaloid the following constitution :—
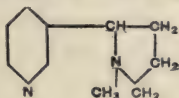
which is that of a β-pyridyl-N-methyl pyrrolidine. The first step taken by Pinner was to oxidize the alkaloid with hydrogen peroxide, and in this way an oxynicotine was obtained of composition $C_{10}H_{14}ON_2$, but no definite ideas as to its structure could be obtained since its decomposition products could not be obtained in an analyzable condition. Again, nicotine could not be regarded as an imide base since acetyl and benzoyl derivatives were not obtainable, although Etard had earlier observed the existence of such derivatives. This discrepancy was explained

by Pinner, who showed that if these acyl derivatives of Etard were hydrolyzed nicotine is not regenerated, but an isomeric base, namely, *meta-nicotine*, is obtained and this has the properties of a secondary base. Consequently, in the formation of Etard's acetyl and benzoyl derivatives the tertiary base, nicotine, is transformed into the isomeric secondary base, meta-nicotine, by the action of the reagents.

Nicotine   Meta-nicotine
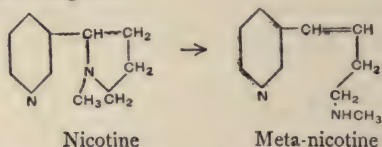
Seeing that oxidation apparently would not give any good results, Pinner next turned his attention to the action of bromine on the alkaloid, and by using a solution of bromine in acetic acid at ordinary temperatures found that a perbromide, $C_{10}H_{10}ON_2Br_2.HBr_3$, is formed, which, on boiling with water, is converted into $C_{10}H_{10}ON_2Br_2$, a compound he called *dibromocotinine*. Again, by heating the alkaloid with bromine dissolved in hydrobromic acid for some hours at $100°$ C., he obtained the hydrobromide of a substance which he designated as *dibromoticonine*, $C_{10}H_8O_2N_2.Br_2HBr$, and it was from the decomposition products of these two basic compounds that the structural formula of the alkaloid was developed. Dibromocotinine, on reduction, yields the parent base cotinine $C_{10}H_{12}ON_2$, and on oxidation yields nicotinic acid, the latter reaction showing that the pyridine complex in the nicotine molecule is unaffected by the action of bromine. Dibromoticonine, on reduction, yields only a monobromo derivative, $C_{10}H_9O_2N_2Br$, and on oxidation also yields nicotinic acid. Now the perbromide which yields dibromcotinine, when boiled with alkalies, yields methylamine, barium oxalate, and a compound, C_7H_7ON, identical with Engler and Kiby's β-pyridyl methyl ketone.

$$C_{10}H_{10}ON_2Br_2 + 3H_2O = CHO.COOH + CH_3.NH_2 + 2HBr + C_5H_4N.CO.CH_3$$

It will be noted that the above equation only allows for the formation of gyloxylic acid, which must undergo further oxidation during the process, and so pass into oxalic acid.

In a similar manner dibromoticonine when heated with baryta yields methylamine, nicotinic acid, and malonic acid, whilst if heated with alkalies in the presence of zinc dust yields methylamine and a derivative $C_9H_{11}O_4N$, which possesses the characteristic properties of an acid.

$$C_{10}H_8O_2N_2Br_2 + 4H_2O = CH_3NH_2 + CH_2(COOH)_2 + 2HBr + C_5H_4N.COOH$$
$$C_{10}H_8O_2N_2Br_2 + 2H_2O + 6H = CH_3NH_2 + 2HBr + C_9H_{11}NO_4$$

Thus we now have that

Dibromocotinine gives	*Dibromoticonine* gives
$C_5H_4N.CO.CH_3$; $C_2H_2O_4$; NH_2CH_3	$C_5H_4N.COOH$; $CH_2(COOH)_2$;
or	CH_3NH_2
$C_5H_4N.C.C- \quad -C-C- \quad -N.CH_3$	or
	$C_5H_4N.C- \quad -C-C-C- \quad -N.CH_3$
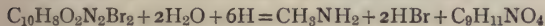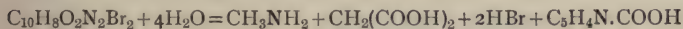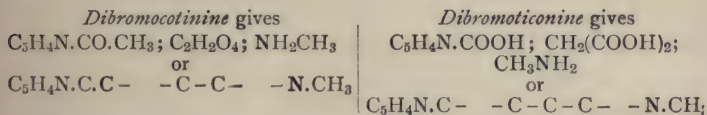
which give for the nucleus of the alkaloid the grouping
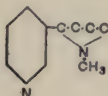
and nicotine is therefore most probably to be represented as
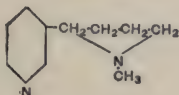
Dibromocotinine is probably a compound of an acid amide type, its structure and decompositions being shown below.
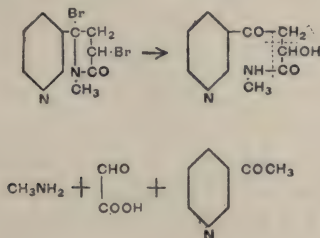
Dibromoticonine similarly is to be represented as

$$CH_2(COOH)_2 + CH_3NH_2 +$$
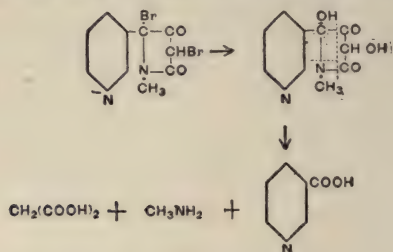
The acid $C_9H_{11}NO_4$ is a pyridyl-$\beta\gamma$-dihydroxybutyric acid, and is formed from dibromoticonine as shown in the annexed scheme.
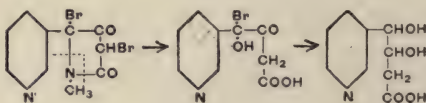
The structure given above by Pinner for nicotine has received confirmation at the hands of Pictet, who has succeeded in synthesizing the alkaloid in the following manner. The mucate of β-aminopyridine on dry distillation is converted into N-β-pyridyl pyrrol, which, when its vapours are passed through a red-hot tube, yields what must be $\alpha\beta$-pyridyl pyrrol since Ciamician has shown that N-alkyl pyrrols by such treatment are transformed into α-alkyl derivatives.

The potassium salt of the $\alpha\beta$-pyridyl pyrrol when heated with methyl iodide yields the methiodide of N-methyl-$\alpha\beta$-pyridyl pyrrol, from which the free base is obtained by distillation over lime. Reduction of this base by means of tin and hydrochloric acid yields a dihydronicotyrine, and this by the action of bromine is transformed into a perbromide. By further reduction of the perbromide *i*-nicotine is obtained.
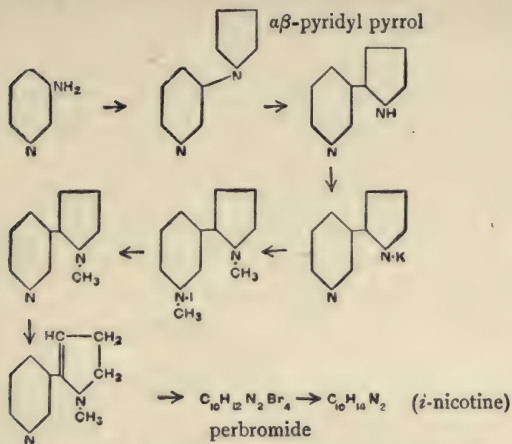
The i-nicotine may be resolved by repeated fractional crystallization of the salt it forms with d-tartaric acid.

Pyrrolidine Group.—The most important derivatives of this group are *atropine*, $C_{17}H_{23}O_3N$, which is found in the roots of the belladonna (*Atropa belladonna*), and *cocaine*, $C_{17}H_{21}O_4N$, found in the leaves of Erythroxylon Coca.

Atropine crystallizes in prisms, and is a strong poison. Its solutions have no action on polarized light. It behaves as a tertiary base and also as an ester, since Lossen showed that on hydrolysis it decomposed into tropic acid and tropine, $C_{17}H_{23}O_3N + H_2O = C_9H_{10}O_3 + C_8H_{15}ON$. Tropic acid also by further heating with baryta water for a considerable time loses a molecule of water, and yields atropic acid, $C_9H_8O_2$, and it is from a study of these products that the structure of the alkaloid has been developed. The constitution of atropic acid (an isomer of cinnamic acid) is shown by its synthesis by Ladenburg and Rügheimer from acetophenone. This ketone is converted in the normal manner by phosphorus pentachloride into the keto-chloride, from which by heating with an alcoholic solution of potassium cyanide a nitrile is formed. This nitrile, on hydrolysis with baryta, is converted into an acid, and by heating the acid,

with hydrochloric acid, alcohol is eliminated and atropic acid is produced.

$$C_6H_5COCH_3 \rightarrow C_6H_5C.Cl_2.CH_3 \rightarrow C_6H_5C(CN)(OC_2H_5)CH_3 \rightarrow$$
$$C_6H_5C(COOH)(OC_2H_5)CH_3 \rightarrow C_6H_5C(:CH_2)COOH.$$
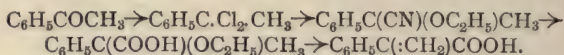
Now, seeing that tropic acid only differs from this acid by the addition of a molecule of water, it must be either

(I) $C_6H_5CH(COOH).CH_2OH$ or   (II) $C_6H_5C(OH)(COOH).CH_3$,
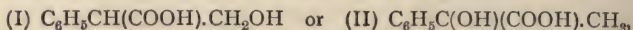
and Fittig and Wurster obtained an isomer of tropic acid (atrolactic acid) by the action of sodium carbonate on the hydrobromic acid addition product of atropic acid. The constitution of this isomer was settled by its synthesis from the cyanhydrin of acetophenone, thus—

$$C_6H_5COCH_3 \rightarrow C_6H_5C(OH)(CN)CH_3 \rightarrow C_6H_5C(OH)(COOH).CH_3,$$
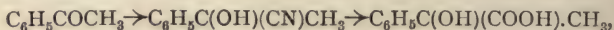
and consequently atrolactic acid is (II) and tropic acid is (I). Further confirmation of this is shown in the synthesis of the latter from the chlorhydrin of atropic acid, which by reduction with zinc and caustic alkali yields tropic acid.

$$C_6H_5C(:CH_2)COOH \rightarrow C_6H_5C(Cl)(CH_2OH)COOH \rightarrow$$
$$C_6H_5.CH(CH_2OH)COOH.$$
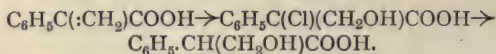
The various splitting products of atropine (derived chiefly from its derivatives tropic acid and tropine), which have been used in elucidating the structure of the alkaloid, are shown in the following chart :—
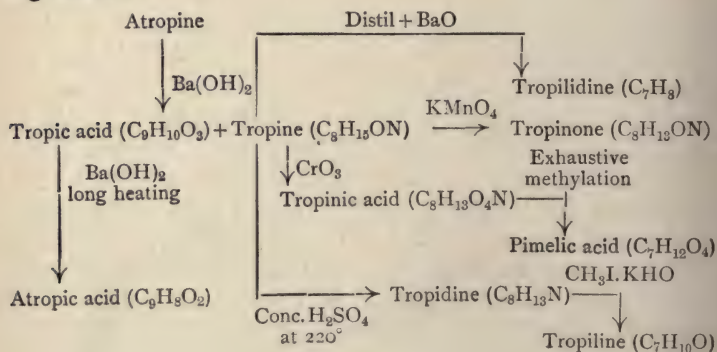
Knowing the structure of tropic acid, it only remains to determine that of tropine (the basic decomposition product of the alkaloid) in order to assign a constitution to atropine, and the earlier work in this direction was carried out by Ladenburg, who showed that tropine, which is an inactive tertiary base, possesses the character of an alcohol, since it unites with acids to form esters, and who also found that the nitrogen atom is attached to a methyl group, because on distillation of tropine with baryta, tropilidine (a hydrocarbon isomeric with toluene) and methylamine are formed—

$$C_8H_{15}ON = H_2O + C_7H_8 + CH_3NH_2$$
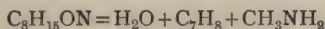
a similar result being obtained if tropine is subjected to the destructive methylation process, the nitrogen atom necessarily in this process being eliminated in the form of trimethylamine.

$$C_7H_{12}O:NCH_3 \xrightarrow{CH_3I} C_7H_{12}O:N(CH_3)_2I \xrightarrow{\text{moist } Ag_2O} C_7H_{12}O:N(CH_3)_2.OH$$
$$C_7H_{11}O:N(CH_3)_3.I \xleftarrow{CH_3I} C_7H_{11}O:N(CH_3)_2 + H_2O \xleftarrow{\text{distil}}$$
$$\longrightarrow C_7H_{11}O:N(CH_3)_3OH \longrightarrow C_7H_8 + 2H_2O + N(CH_3)_3$$
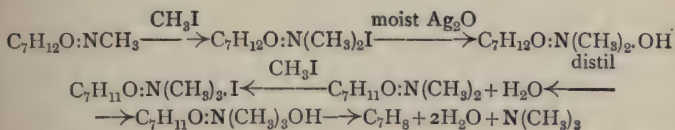
Ladenburg next developed his ideas as to structure from the non-oxygenated compound tropidine ($C_8H_{13}N$), obtained when tropine is heated with concentrated sulphuric acid, and showed that it was an unsaturated compound. This substance forms a hydrobromide, which reacts with a large excess of bromine to give $\beta\beta^1$-dibromopyridine, and so it was concluded that tropidine is a partially reduced pyridine with an unsaturated side chain of two carbon atoms, the latter fact being shown by the formation of ethylene dibromide when the reaction product of bromine and tropidine hydrobromide is heated to about 170° C. The side chain was then shown to be in the α-position by the conversion of tropine into α-ethyl-pyridine by a somewhat complicated series of reactions, and Ladenburg finally concluded that tropidine and tropine possessed the following structures :—

CH:CH.C.CH:CH$_2$
| 3H ‖
CH:CH.N.CH$_3$
Tropidine

CH:CH.C.CHOH.CH$_3$
| 3H ‖
CH:CH.N.CH$_3$

or

↓

CH:CH.C.CH$_2$CHOH
| 3H ‖
CH:CH.N.CH$_3$
Tropine
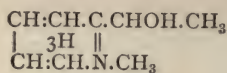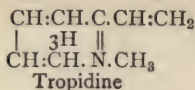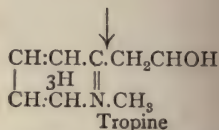
Various objections can be urged against the above formulæ, the most important perhaps being those of Merling, that tropine can be made to yield hydroaromatic derivatives (although in the light of later work these appear to be cycloheptane derivatives), and that on oxidation with chromic acid it yields the dibasic tropinic acid, which would seem to be an unlikely product if the tropine molecule contained one side chain only.

By distilling the acid over lime, Merling obtained what he thought was N-methyl piperidine, and considered that tropinic acid was N-methyl piperidine-$\alpha\beta$-dicarboxylic acid $C_6H_{11}N$(COOH)$_2$. Further, he found that tropilidene on oxidation yielded benzaldehyde and benzoic acid, and that its dibromide when heated decomposed into hydrobromic acid and benzyl bromide, reactions which were explained by assigning to it the structure of a methylene dihydro-benzene. Acting on the assumption that a reduced benzene ring is present in the tropine molecule, and that a reduced pyridine ring is also present, as is shown in the reactions mentioned above, Merling proposed the following formula for tropine,

CH$_2$.CH——CH$_2$
| CHOH |
| CH$_2$ |
CH$_2$.CH——NCH$_3$
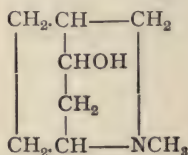
which allows for the production of a dibasic acid on oxidation, for the formation of hydroaromatic derivatives by elimination of nitrogen, and also for the production of pyridine derivatives by the breaking down of the reduced benzene ring.

The constitution of tropine was, however, finally settled by the brilliant investigations of Willstätter (1896-1901), in which it was shown that tropine is a cycloheptane derivative containing a

nitrogen bridge system. The starting-point in this work was the ketonic compound tropinone, $C_8H_{13}ON$, obtained in the oxidation of tropine with chromic acid or with lead peroxide. This ketone, of course, necessarily arises from the oxidation of the group $-CHOH-$ to $-CO-$, and Willstätter found that it formed a dibenzal derivative on treatment with benzaldehyde in presence of hydrochloric acid; a mono- and a di-oxalic ester derivative; a di-isonitroso derivative; and a diphenyl hydrazone of tropanetrione on treatment with benzene diazonium chloride, all of which reactions go to show the presence of the grouping $-CH_2-CO-CH_2-$ in the molecule and not, as in the case of Merling's formula of $-CH-CO-CH_2-$. These reactions thus lead to a modification of Merling's formula for tropine, and give rise to the following three possibilities for tropine :—

A decision as to which was correct was arrived at by using the destructive methylation process on tropinic acid, when a piperylene dicarboxylic acid was obtained, which, on reduction, gave pimelic acid, $HOOC(CH_2)_5.COOH$, showing that an unbranched chain of seven carbon atoms exists in the tropine molecule, a condition only fulfilled by formula (II) above. These reactions may be shown as follows :—

10

Consequently tropinic acid is the $\alpha\alpha^1$-carboxy-acetic acid of N-methylpyrrolidine. These results thus allow of the formulation of tropine and its derivatives, and also of atropine, as cycloheptane compounds, in the following manner :—

Atropine → Tropine

Tropidine

Tropinone
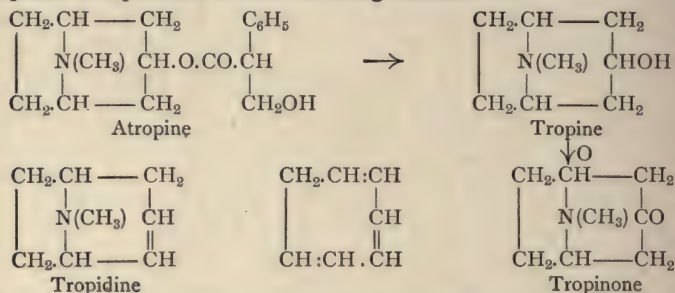
Confirmation of the above structural formula for tropine was given later by Willstätter in two papers in 1901, the first dealing with the synthesis of tropidine from suberone, and the second showing the conversion of tropidine into tropine. These syntheses were carried out in the following manner. Suberone on reduction passes into suberyl alcohol, which is then converted into suberyl iodide, and this by the action of alcoholic potash yields a cycloheptene, similar results following by conversion of suberone into its oxime, reduction of the oxime to the amine, and exhaustive methylation of the amine.
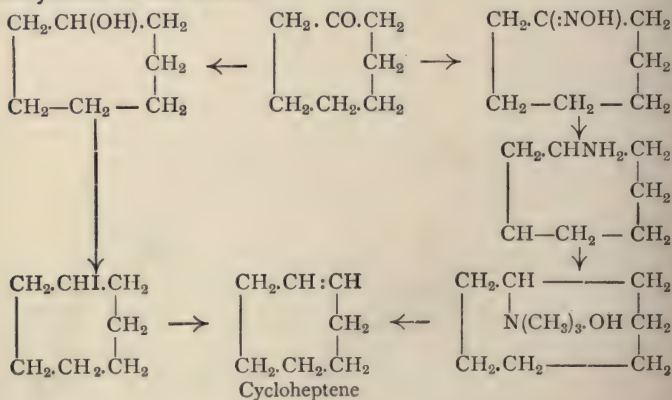
Cycloheptene

The dibromide of this hydrocarbon when heated with dimethyl-
amine is converted into Δ^2-dimethylamidocycloheptene, from
which by destructive methylation and distillation of the hydroxide,
cycloheptadiene is obtained. Cycloheptadiene also forms a di-
bromide, the bromine atoms, in accordance with Thiele's observa-
tions, uniting with the carbon atoms in the 1.4 position of the
conjugate system, and the dibromide, when heated with quinoline
to 150-165° C., is converted into cycloheptatriene, identical with
the tropilidene obtained from tropine.

$$
\begin{array}{ccc}
\text{CH}_2.\text{CHBr.CHBr} & \text{CH}_2.\text{CH}_2\underline{\quad\quad}\text{CH} & \text{CH}_2.\text{CH}_2\underline{\quad\cdot\quad}\text{CH} \\
\mid\quad\quad\quad\mid & \mid\quad\quad\quad\parallel & \mid\quad\quad\quad\parallel \\
\mid\quad\text{CH}_2 \rightarrow & \mid\quad\text{N(CH}_3)_2\ \text{CH} \rightarrow & \mid\quad\text{N(CH}_3)_3.\text{OH CH} \\
\mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid \\
\text{CH}_2.\text{CH}_2.\text{CH}_2 & \text{CH}_2.\text{CH}_2\underline{\quad\quad}\text{CH}_2 & \text{CH}_2.\text{CH}_2\underline{\quad\quad}\text{CH} \\
& & \downarrow
\end{array}
$$

$$
\begin{array}{ccc}
\text{CH.CH:CH} & \text{BrCH . CH : CH} & \text{CH : CH . CH} \\
\parallel\quad\quad\mid & \mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid \\
\parallel\quad\text{CH} \leftarrow & \mid\quad\text{CHBr} \leftarrow & \mid\quad\text{CH} \\
\mid\quad\quad\parallel & \mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid \\
\text{CH.CH}_2.\text{CH} & \text{CH}_2.\text{CH}_2.\text{CH}_2 & \text{CH}_2.\text{CH}_2.\text{CH}_2 \\
\text{Tropilidine}
\end{array}
$$
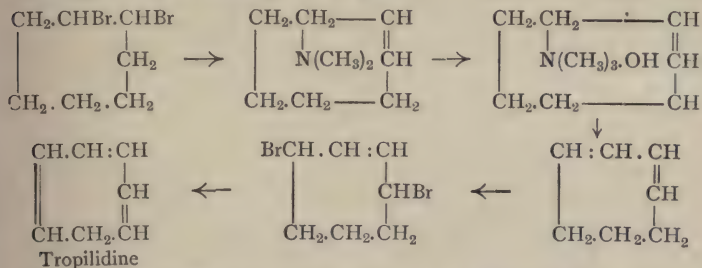
This yields a monohydrobromide, which is converted by dimethyl-
amine into dimethylamidocycloheptadiene, reduction of the latter
leading to the formation of a corresponding heptene. This
substance, on treatment with bromine in hydrobromic acid
solution, is converted into a dibromide which, on purification,
rearranges itself into the methyl bromide of bromo-tropane.

$$
\begin{array}{ccc}
\text{CH}_2.\text{CHBr.CH}_2 & \text{CH}_2.\text{CH}\underline{\quad\quad}\text{CH}_2 & \text{CH}_2.\text{CH}\underline{\quad\quad}\text{CH}_2 \\
\mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid \\
\mid\quad\text{CH} \rightarrow & \mid\quad\text{N(CH}_3)_2\ \text{CH} \rightarrow & \mid\quad\text{N(CH}_3)_2\ \text{CH}_2 \\
\mid\quad\parallel & \mid\quad\quad\quad\parallel & \mid\quad\quad\quad\mid \\
\text{CH:CH---CH} & \text{CH:CH}\underline{\quad\quad}\text{CH} & \text{CH}_2.\text{CH}=\text{CH} \\
& & \downarrow
\end{array}
$$

$$
\begin{array}{cc}
\text{CH}_2\underline{\quad}\text{CH}\underline{\quad\quad}\text{CH}_2 & \text{CH}_2.\text{CH}\underline{\quad\quad}\text{CH}_2 \\
\mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid \\
\mid\quad\text{Br.N(CH}_3)_2\ \text{CH}_2 \leftarrow & \mid\quad\text{N(CH}_3)_2\ \text{CH}_2 \\
\mid\quad\quad\quad\mid & \mid\quad\quad\quad\mid \\
\text{CH}_2\text{---CH}\underline{\quad\quad}\text{CHBr} & \text{CH}_2.\text{CHBr---CHBr}
\end{array}
$$
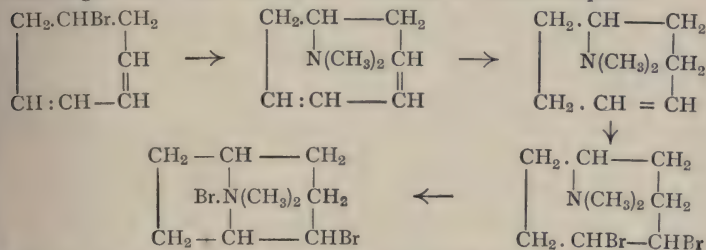
The bromide so produced is then converted into the correspond-
ing methyl iodide of tropidine by eliminating hydrobromic acid
(through the agency of sodium hydroxide), and subsequent addi-
tion of potassium iodide to the solution, to replace the bromine

atom attached to the nitrogen; and the iodide into the chloride by digestion with silver chloride, the chloride on heating losing methyl chloride and giving tropidine.

$$
\begin{array}{ccc}
\begin{array}{l}
CH_2.CH \underline{\quad\quad} CH_2 \\
\quad | \qquad\qquad | \\
Cl.N(CH_3)_2 \; CH \\
\quad | \qquad\qquad \| \\
CH_2.CH \underline{\quad\quad} CH
\end{array}
& \longrightarrow &
\begin{array}{l}
CH_2\,CH \underline{\quad\quad} CH_2 \\
\quad | \qquad\qquad | \\
\quad N(CH_3) \; CH \\
\quad | \qquad\qquad \| \\
CH_2\,CH \underline{\quad\quad} CH
\end{array}
\end{array}
$$

The conversion of tropidine into tropine then follows by heating tropidine hydrobromide with water or dilute sulphuric acid to 200° C., when ψ-tropine is obtained. Oxidation of this to tropinone and subsequent reduction with zinc dust and hydriodic acid finally yielded tropine—

$$
\begin{array}{l}
CH_2.CH \underline{\quad} CH_2 \\
\quad | \qquad\qquad | \\
\quad N(CH_3) \; CHBr \qquad\rightarrow \\
\quad | \qquad\qquad | \\
CH_2.CH \underline{\quad} CH_2
\end{array}
$$

ψ-Tropine
$$
\begin{array}{l}
CH_2.CH \underline{\quad} CH_2 \\
\quad | \qquad\qquad | \\
\quad N(CH_3) \; CHOH \\
\quad | \qquad\qquad | \\
CH_2.CH \underline{\quad} CH_2 \\
\qquad\qquad \downarrow
\end{array}
$$

$$
\begin{array}{l}
CH_2.CH \underline{\quad} CH_2 \\
\quad | \qquad\qquad | \\
\quad N(CH_3) \; CHOH \qquad \leftarrow \\
\quad | \qquad\qquad | \\
CH_2.CH \underline{\quad} CH_2 \\
\qquad Tropine
\end{array}
$$

$$
\begin{array}{l}
CH_2.CH \underline{\quad} CH_2 \\
\quad | \qquad\qquad | \\
\quad N(CH_3) \; CO \\
\quad | \qquad\qquad | \\
CH_2.CH \underline{\quad} CH_2
\end{array}
$$
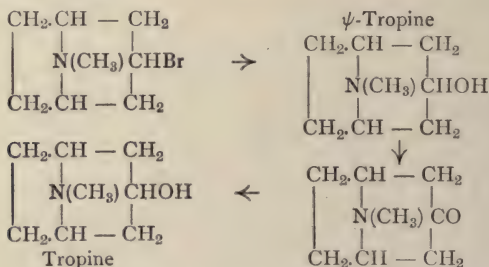
Cocaine, $C_{17}H_{21}O_4N$, is one of a number of alkaloids found in the leaves of Erythroxylon coca. It crystallizes in prisms, melting at 97-98° C., and sublimes with partial decomposition at a somewhat higher temperature. Its solutions react alkaline, and are laevo-rotatory. On hydrolysis it yields benzoyl ecgonine, $C_{16}H_{19}NO_4$, and methyl alcohol, the former product being in its turn decomposed on treatment with acids or alkalies into ecgonine and benzoic acid. Thus it appears that cocaine is an ester, and may be considered as a methyl benzoyl ecgonine, $C_8H_{13}N(O.COC_6H_5)COOCH_3$. It is also a tertiary base, and contains an $-N.CH_3$ group, since Merck has stated that ecgonine which may be considered as the parent substance of cocaine, when distilled over nearly dry barium hydroxide, yields methylamine.

Since hydrolysis of cocaine ultimately leads to ecgonine, it

suffices to determine the structure of the latter compound in order to arrive at the constitution of the alkaloid. This has been arrived at by showing the relation that exists between ecgonine and tropine. Ecgonine has the characters of an acid, a base and an alcohol, since it can form esters, quaternary ammonium salts, and acyl derivatives, consequently it may be represented as $N:C_8H_{13}(OH)COOH$, and as it also contains the $-N.CH_3$ group, as mentioned above, this formula may be developed into $CH_3.N:C_7H_{10}(OH).COOH$. The relation between ecgonine and tropine was first shown in the following manner. Ecgonine, when heated with phosphorus oxychloride or pentachloride, loses a molecule of water and passes into *anhydroecgonine*, $C_9H_{13}O_2N$, which, when heated under pressure with hydrochloric acid to 280°, decomposes into carbon dioxide and tropidine, $C_8H_{13}N$; and consequently anhydroecgonine is to be considered as a tropidine carboxylic acid. Further confirmation of the relation existing between ecgonine and tropine is given by Willstätter's observations that both substances yield the same oxidation products, namely tropinone and tropinic acid. Thus by comparison of the formulæ of the two compounds, viz., $C_9H_{15}O_3N$ and $C_8H_{15}ON$, it would seem that ecgonine might be considered as a carboxylic acid of tropine, with its carboxyl group attached to the carbon atom adjacent to the group $-CH.OH-$, since oxidation yields tropinic acid, a N-methyl pyrrolidine derivative, showing that the complex

$$\begin{array}{c} CH_2-CH- \\ \quad\quad\quad | \\ \quad\quad\quad N.CH_3 \\ \quad\quad\quad | \\ CH_2-CH- \end{array}$$
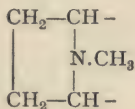
is not affected by oxidation, and that, therefore, the carboxyl group in ecgonine cannot be present in that part of the molecule.

The two most important decomposition products of ecgonine are anhydroecgonine, $C_9H_{13}O_2N$, and hydroecgonidine, $C_9H_{15}O_2N$, the former, as already mentioned, being a tropidine carboxylic acid, which is converted into hydroecgonidine by reduction with sodium and amyl alcohol. Anhydroecgonine contains the carboxyl

group of ecgonine and is formed by the elimination of water from the group $- CHOH - CH_2 -$ of ecgonine, thus giving rise to the grouping $- CH = CH -$, as in tropidine, or as an alternative to the grouping $- C(COOH) = CH -$. The choice between the two alternatives was derived in the following manner. Einhorn, by destructive methylation of anhydroecgonine, obtained an acid that he described as *p*-methylene dihydrobenzoic acid, $C_8H_8O_2$, and which on reduction was converted into the so-called Δ^1—ethyl-cyclopentane carboxylic acid, $C_8H_{12}O_2$. This acid was later shown to be identical with the cycloheptene carboxylic acid obtained from suberone by the addition of hydrocyanic acid and subsequent hydrolysis of the resulting nitrile to hydroxysuberane carboxylic acid. The elimination of water from this acid gives rise to a cycloheptene carboxylic acid identical with the above Δ^1-ethylcyclopentane carboxylic acid, thus—

$$
\begin{array}{ccc}
\underset{\displaystyle CH_2.CH_2.CH_2}{\overset{\displaystyle CH_2.CH_2.CH_2}{\big|\ \ CO\ \ \big|}} & \rightarrow & \underset{\displaystyle CH_2.CH_2.CH_2}{\overset{\displaystyle CH_2.CH_2.CH_2}{\big|\ C(OH)CN\ \big|}} \\
 & & \downarrow \\
\underset{\displaystyle CH_2.CH_2.CH}{\overset{\displaystyle CH_2.CH_2.CH_2}{\big|\ \overset{\parallel}{C}.COOH\ \big|}} & \leftarrow & \underset{\displaystyle CH_2.CH_2.CH_2}{\overset{\displaystyle CH_2.CH_2.CH_2}{\big|\ C(OH).COOH\ \big|}}
\end{array}
$$

and thus *p*-methylene dihydrobenzoic acid, which contains four hydrogen atoms less, must be the corresponding cycloheptatriene carboxylic acid—

$$
\underset{\displaystyle CH:CH.CH}{\overset{\displaystyle CH:CH.CH.COOH}{\big|\ \overset{\parallel}{CH}\ \big|}}
$$

for Willstätter has shown that this acid is transformed by alkalies into an isomer in which the double bond is adjacent to the $- COOH$ group, and so in the above compound it cannot be in such a position, and consequently in anhydroecgonine cannot be adjacent to the carboxyl group. Thus anhydroecgonine and hydroecgonidine must be—

$$
\begin{array}{ccc}
\text{CH}_2.\text{CH} - \text{CH.COOH} & & \text{CH}_2.\text{CH} - \text{CH.COOH} \\
\mid \qquad \mid & \text{and} & \mid \qquad \mid \\
\text{N.CH}_3\ \text{CH} & & \text{N(CH}_3)\ \text{CH}_2 \\
\mid \qquad \parallel & & \mid \qquad \mid \\
\text{CH}_2.\text{CH} - \text{CH} & & \text{CH}_2.\text{CH} - \text{CH}_2
\end{array}
$$

Further confirmation of the presence of the cycloheptane ring in the ecgonine molecule was given in 1898 by Willstätter, who showed that hydroecgonidine could be broken down to suberone in the following manner. The destructive methylation of hydroecgonidine ethyl ester leads to the formation of an unsaturated nitrogen compound which, when heated with alkalies, yields an unsaturated acid, C_7H_9COOH.

$$
\begin{array}{ccccc}
\text{CH}_2.\text{CH} - \text{CH.COOR} & & \text{CH}_2.\text{CH:C.COOR} & & \\
\mid \qquad \mid & & \mid & & \\
\text{N(CH}_3)\ \text{CH}_2 & \rightarrow & \text{CH}_2 & \rightarrow & C_7H_9COOH \\
\mid \qquad \mid & & \mid & & \\
\text{CH}_2.\text{CH} - \text{CH}_2 & & \text{CH}_2.\text{CH.CH}_2 & & \\
& & \mid & & \\
& & \text{N(CH}_3)_2 & &
\end{array}
$$
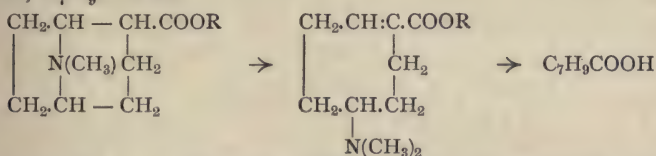
This acid on reduction passes into the saturated acid, $C_7H_{13}COOH$, which on bromination by the Hell-Volhard method, brominates in the α-position. On treatment with baryta water the bromo-acid yields two products, one arising by loss of hydrobromic acid, and consequently being an unsaturated acid, $C_7H_{11}.COOH$, the other being an hydroxy-acid formed by replacement of bromine by the hydroxyl group. Oxidation of the hydroxy-acid with lead peroxide converts it into suberone, $C_7H_{12}O$, thus showing the presence of the cycloheptane ring in the ecgonine molecule. The acid, C_7H_9COOH, is thus a cycloheptadiene carboxylic acid, probably of the annexed structure, but the positions of the double bonds are only conjectural. The cycle of reactions is shown thus—

$$
\begin{array}{ccccc}
\text{CH}_2.\text{CH:CH} & & \text{CH}_2.\text{CH}_2.\text{CH}_2 & & \text{CH}_2.\text{CH}_2.\text{CH}_2 \\
\mid \qquad \quad & \xrightarrow{\text{H}} & \mid \qquad \quad & \xrightarrow{\text{Br}} & \mid \\
\text{CH.COOH} & & \text{CH.COOH} & & \text{C.Br.COOH} \\
\mid \qquad \quad & & \mid \qquad \quad & & \mid \\
\text{CH}_2.\text{CH:CH} & & \text{CH}_2.\text{CH}_2.\text{CH}_2 & & \text{CH}_2.\text{CH}_2.\text{CH}_2
\end{array}
$$

$$
\downarrow \text{Ba(OH)}
$$

$$
\begin{array}{ccccc}
\text{CH}_2.\text{CH}_2.\text{CH}_2 & & & & \text{CH}_2.\text{CH}_2.\text{CH}_2 \\
\mid \qquad \quad & & \xleftarrow{\text{PbO}_2} & & \mid \\
\text{CO} & & & & \text{C(OH).COOH} \\
\mid \qquad \quad & & & & \mid \\
\text{CH}_2\text{CH}_2.\text{CH}_2 & & & & \text{CH}_2.\text{CH}_2.\text{CH}_2
\end{array}
$$
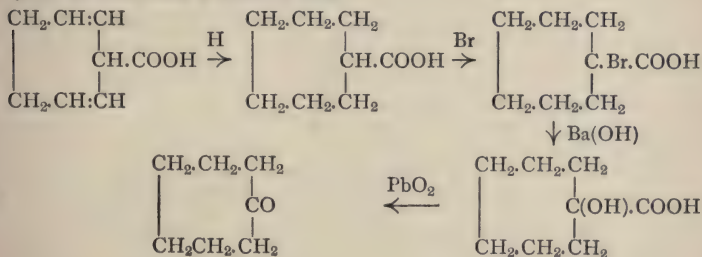
Isoquinoline Group.—This group includes principally the *opium alkaloids* obtained from the sap of various members of the Papaveraceæ; *berberine*, $C_{20}H_{17}O_4N$, and *hydrastine*, $C_{21}H_{21}O_6N$, obtained from the root of the golden seal (*Hydrastis canadensis*), and *corydaline*, $C_{22}H_{27}O_4N$, obtained from the root of *Corydalis cara*. The opium alkaloids may for convenience be divided into two groups, namely, the papaverine group, containing *papaverine*, $C_{20}H_{21}O_4N$, *laudanosine*, $C_{21}H_{27}O_4N$, and *narcotine*, $C_{22}H_{23}O_7N$, as members which have been most thoroughly investigated; and the morphine group, containing *morphine*, $C_{17}H_{19}O_3N$, *codeïne*, $C_{18}H_{21}O_3N$, and *thebaine*, $C_{19}H_{21}O_3N$.

Papaverine Sub-group.—*Papaverine*, $C_{20}H_{21}O_4N$, was first discovered by Merck in 1848. It crystallizes in prisms which melt at 147°, and is a weak, inactive base. The constitution of this alkaloid has been determined in the following manner. The Zeisel reaction shows that four methoxy-groups are present, since it is found that four molecules of methyl iodide are obtained by the decomposition of one molecule of the alkaloid, and again fusion with caustic alkali converts it into dimethylhomopyrocatechin, $CH_3.(1).C_6H_4(OCH_3)_2(3-4)$, and a base, $C_{11}H_{11}O_2N$, which on oxidation yields cinchomeronic acid, $C_5H_3N(COOH)_2$, and an acid, $C_{10}H_{10}O_6$, that was found to be an isomer of hemipinic acid, and was consequently designated as metahemipinic acid. This latter acid was found to be dibasic, and as it formed both an imide and an anhydride, it followed that the carboxyl groups must be in the ortho position to each other. Also, since on fusion with alkali the acid is transformed into catechol, $C_6H_4(OH)_2(1.2)$, the methoxy groups must be in the orthoposition to each other, and so the acid must be represented as—
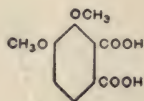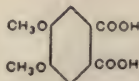
(I)   (II)

but as it is known that hemipinic acid is (I), metahemipinic acid must be (II). Thus having the two complexes—
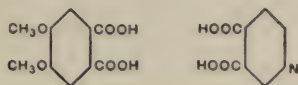
it would seem that the base, $C_{11}H_{11}O_2N$, which on oxidation yields these two products, should be a dimethoxyisoquinoline,
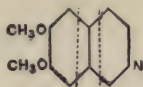
oxidation taking place as shown by the dotted lines, in the one case yielding the nitrogen free dibasic acid, by destruction of the pyridine ring; and in the other case the pyridine dicarboxylic acid by destruction of the benzene ring. Finally, it is now necessary to unite this group with the dimethylhomopyrocatechin molecule in order to arrive at the structure of the alkaloid. The point of union seems to be the α-carbon atom of the isoquinoline complex, for, on oxidation with potassium permanganate, papaverine yields an acid, $C_{12}H_{12}O_4N$, which, on further oxidation, is converted into metahemipinic acid, and α-carbocinchomeronic acid, $C_5H_2N(COOH)_3(\alpha\beta\gamma)$. Thus the alkaloid may be formulated as—
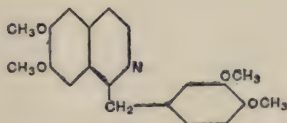
a structure which has been confirmed by Pictet's recent synthesis of the alkaloid, as follows. Veratrol, by the action of acetyl chloride, is converted into aceto-veratrone, the isonitroso-derivative of which on reduction with stannous chloride and hydrochloric acid is transformed into amino-acetoveratrone hydrochloride—

$$C_6H_4(OCH_3)_2 \longrightarrow CH_3.CO.C_6H_3(OCH_3)_2 \longrightarrow (CH_3O)_2.C_6H_3.CO.CH:NOH$$
$$\downarrow$$
$$(CH_3O)_2.C_6H_3.CO.CH_2.NH_2.HCl$$
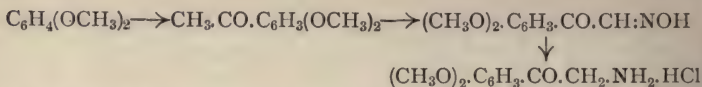
As a second starting-point vanillin is taken and by methylation converted into methyl vanillin, from which the cyanhydrin is formed in the usual manner, and is then simultaneously hydrolysed and reduced by hydriodic acid to homoprotocatechuic acid. This acid on methylation is converted into homoveratric acid, and the latter into homoveratroyl chloride—

$$
\begin{array}{lcl}
(CH_3O)(HO).C_6H_3.CHO & \longrightarrow & (CH_3O)_2.C_6H_3.CHO \\
& & \downarrow \\
(HO)_2.C_6H_3.CH_2.COOH & \longleftarrow & (CH_3O)_2.C_6H_3.CHOH.CN \\
\downarrow & & \\
(CH_3O)_2.C_6H_3.CH_2.COOH & \longrightarrow & (CH_3O)_2.C_6H_3.CH_2.COCl
\end{array}
$$
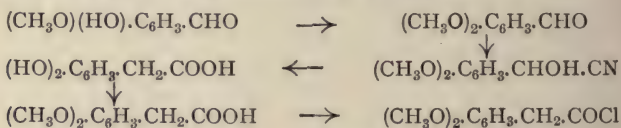
Now homoveratroyl chloride and amino-acetoveratrone hydrochloride condense in the presence of caustic potash to yield homoveratroyl-aminoacetoveratrone, which on reduction in alcoholic solution by sodium amalgam is converted into homoveratroyl-hydroxyhomoveratrylamine. On heating the latter compound in xylene solution with phosphorus pentoxide, it loses water and is transformed into papaverine.
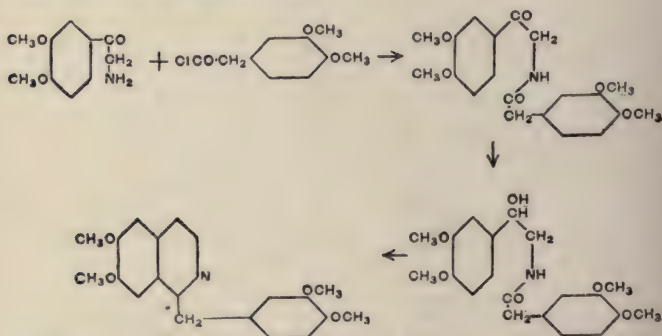
Laudanosine, $C_{21}H_{27}O_4N$, was first isolated in 1871 by Hesse. Its relation to papaverine was shown by Pictet, who reduced the methochloride of papaverine to racemic laudanosine, and separated the racemic mixture into its components by quinic acid, the

δ-N methyltetrahydro-papaverine so obtained being identical with laudanosine. This reaction may be illustrated in the following manner :—
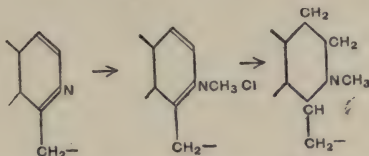
The correctness of this view was again shown by Pictet in 1909 by the synthesis of the alkaloid from eugenol and vanillin in the following manner. Methyl vanillin, when subjected to the Perkin reaction, yields dimethylcaffeic acid, which is then reduced to dimethylhydrocaffeic acid, the amide of the latter, under the influence of bromine and caustic potash, being converted into homoveratrylamine.

$$(CH_3O)_2.C_6H_3.CHO \longrightarrow (CH_3O)_2.C_6H_3.CH:CH.COOH$$
$$\downarrow$$
$$(CH_3O)_2.C_6H_3.CH_2.CH_2.CONH_2 \longleftarrow (CH_3O)_2.C_6H_3.CH_2.CH_2.COOH$$
$$\downarrow$$
$$(CH_3O)_2.C_6H_3.CH_2.CH_2.NH_2$$
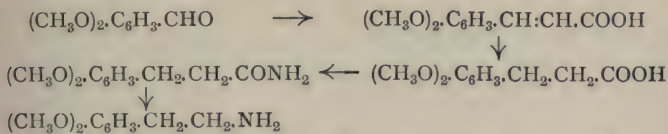
Eugenol is acetylated and the acetyl compound oxidized by potassium permanganate, when acetyl-homovanillic acid is formed. This acid on hydrolysis and subsequent methylation yields homoveratric acid, which is then converted into the acid chloride.

$$\overset{O}{CH_2:CH.CH_2.C_6H_3(OCOCH_3).OCH_3} \rightarrow HOOC.CH_2.C_6H_3(OCOCH_3).OCH_3$$
$$\downarrow$$
$$HOOC.CH_2.C_6H_3(OCH_3)_2 \longleftarrow HOOC.CH_2.C_6H_3(OH).OCH_3$$
$$\downarrow$$
$$(CH_3O)_2.C_6H_3.CH_2.COCl$$
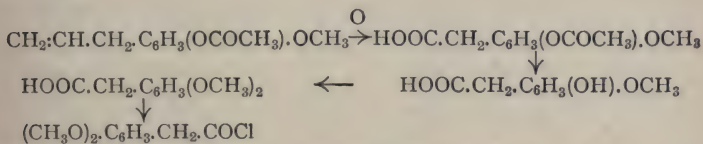
By condensation of the acid chloride with the amine in the presence of caustic alkali, homoveratroyl-homoveratrylamine is produced, which, when heated with phosphorus pentoxide and xylene, yields dihydropapaverine. The dihydropapaverine is then converted into the methiodide and the methyl derivative finally reduced by tin and hydrochloric acid to *dl*-laudanosine.
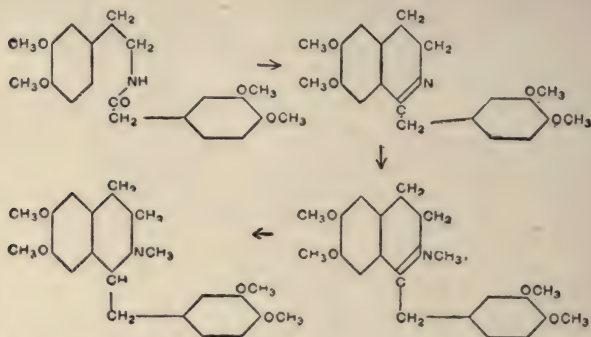
Narcotine, $C_{22}H_{23}O_7N$, is a weak tertiary base, which is insoluble in cold solutions of the caustic alkalies, but is soluble in hot solutions of the alkalies, the salts obtained being formed by the splitting of a lactone ring in the molecule, with consequent assumption of the elements of water. It may be shown by application of the usual reactions that three methoxy groups are present, and also that the nitrogen atom is in combination with a methyl group. The chief decomposition products obtained from narcotine are opianic acid, $C_{10}H_{10}O_5$, and hydrocotarnine, $C_{12}H_{15}O_3N$, which are formed as products of hydrolysis; meconine, $C_{10}H_{10}O_4$, and hydrocotarnine, obtained on reduction; and opianic acid and cotarnine, $C_{12}H_{15}NO_4$, produced when the alkaloid is oxidized with nitric acid.

Hemipinic acid, $C_{10}H_{10}O_6$, opianic acid, $C_{10}H_{10}O_5$, and meconine, $C_{10}H_{10}O_4$, are three compounds, which are intimately related, since oxidation of opianic acid yields hemipinic acid, and reduction yields meconine. They are thus related as dibasic acid, aldehyde acid, and internal anhydride of the corresponding alcohol acid. Hemipinic acid is dibasic, and gives an anhydride, consequently its carboxyl groups must be in the ortho-position to each other. It contains two methoxy groups, and on heating with hydriodic acid gives protocatechuic acid, $HOOC(1).C_6H_3.(OH)_2(3.4)$. Thus it must be either
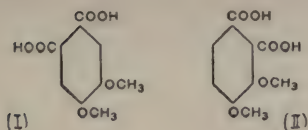
but, as Wegscheider showed that on esterification it could yield *two* different monomethyl esters, it must be (II), for (I) is a symmetrical compound, and could give but one ester. Confirmation of the above structure is given by Lagodzinski's synthesis of alizarine from hemipinic acid and benzene in the presence of aluminium chloride, the reaction product passing into alizarine on subsequent treatment with concentrated sulphuric acid.
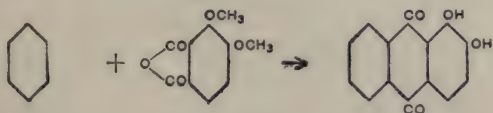
Now, opianic acid, which is a monobasic acid and an aldehyde, and also contains two methoxyl groups, must be either
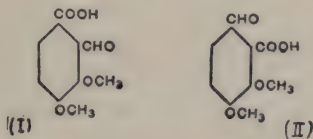
and of these alternatives (II) is correct, for, when heated with hydrochloric acid, opianic acid gives isovanillin, $OHC(1).C_6H_3.(OH)(OCH_3)(3.4)$, or, when distilled over soda lime, gives methyl vanillin, $OHC(1).C_6H_3.(OCH_3)_2(3.4)$, which is only possible with a compound of the structure given in (II). Meconine has been synthesized by Fritsch, and its structure as the internal anhydride of the alcohol acid thus confirmed. In this synthesis the methyl ester of 2.3-dimethoxybenzoic acid is condensed with chloral hydrate in the presence of sulphuric acid, and the resulting phthalide derivative hydrolyzed to a hydroxy-acid, which when heated loses water and carbon dioxide and forms meconine,
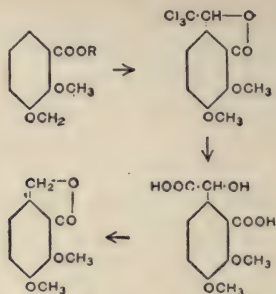
Cotarnine, $C_{12}H_{15}O_4N$, is a secondary base and also an aldehyde, and contains one methoxy group. Its salts are of the type $C_{12}H_{13}O_3N.HCl$, which shows that water is eliminated in their formation, and that their structure is thus different from that of the parent substance. Cotarnine, on oxidation with nitric acid, yields apophyllenic acid, $C_8H_7O_4N$, whose structure, as the methyl betaine of cinchomeronic acid, was shown by its synthesis by Roser on heating the methiodide of cinchomeronic acid.

$$HOOC.C_5H_3N(CH_3I).COOH \rightarrow OC.C_5H_3N(CH_3).COOH.$$
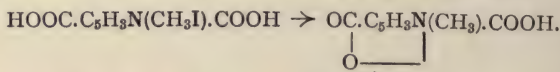
but beyond showing in this way the possibilities of a pyridine ring in cotarnine, nothing further was elucidated by the above oxidation process. Further ideas as to the structure, however, were obtained by the destructive methylation of the base, when an unsaturated aldehyde cotarnone, $C_{11}H_{10}O_4$, was produced, from which the dibasic cotarnic acid, $C_8H_6O_2(COOH)_2$, was obtained by oxidation with potassium permanganate.

$$C_{11}H_{11}O_4.NHCH_3 \xrightarrow{CH_3I} C_{11}H_{11}O_4.N(CH_3)_3I$$
$$\downarrow NaOH$$
$$N(CH_3)_3 + NaI + H_2O + C_{11}H_{10}O_4.$$
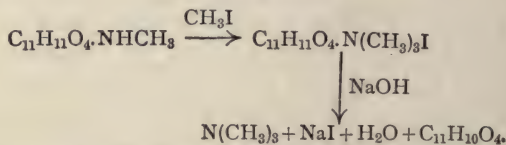
Now, since cotarnic acid forms an anhydride, contains a methoxy group, and on reduction with phosphorus and hydriodic acid yields gallic acid, it must be either

(II)
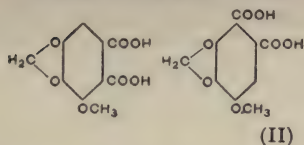
The recent synthesis of cotarnic acid by W. H. Perkin has shown that the acid must possess the structure represented by the formula (I). The starting point in this synthesis is methylene dioxyphenyl propionic acid, which condenses in the presence of phosphorus pentoxide to 5.6-methylene dioxy-1-hydrindone. This latter compound is then nitrated, reduced to the amino-derivative, and the amino-group replaced by the hydroxyl group in the usual manner, a considerable loss of material, however, taking place at this stage of the operations. The hydroxy-compound is then methylated by means of dimethyl sulphate, and the methyl ether condensed with piperonal, by the agency of caustic alkali. The piperonyl compound on oxidation with potassium permanganate yielded cotarnic acid, which was recognized by its characteristic methyl-imide.
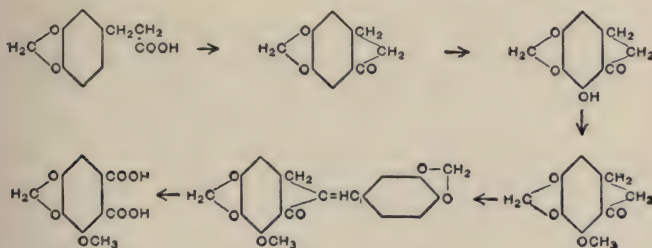
Thus cotarnone and cotarnine are respectively
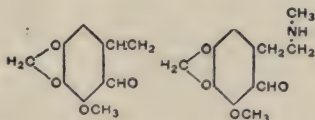
This structural formula of cotarnine has recently (1910) been confirmed by Salway, who has succeeded in synthesizing the base

from myristicin as follows. By oxidation of myristicin, myristicin-aldehyde is obtained, and is then converted into 3-methoxy-4.5-methylene dioxycinnamic acid. This acid is now reduced to the corresponding phenyl propionic acid, which is next transformed into its amide, and the latter converted by the Hofmann reaction into 3-methoxy-4.5-methylenedioxyphenylethylamine. The phenyl acetyl derivative of this base is then heated (in xylene solution) with phosphoric anhydride, and two isomeric dihydro-isoquinoline derivatives are obtained. These may be separated by the fractional recrystallization of their hydrochlorides, and the 8-methoxy-6.7-methylenedioxy-1-benzyl-3.4-dihydroisoquinoline so obtained, when converted into its methochloride, and subsequently reduced with tin and hydrochloric acid, yielded 1-benzyl-hydrocotarnine. On oxidation of the benzyl compound with manganese dioxide and sulphuric acid, cotarnine is formed.
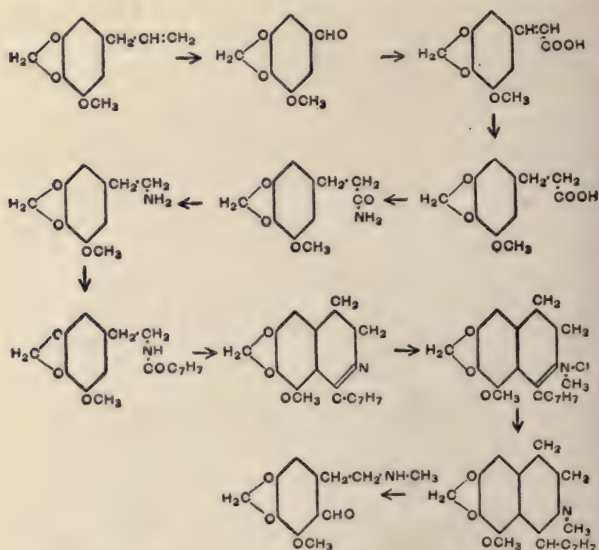
The hydrochloride of cotarnine would consequently be formed thus :—
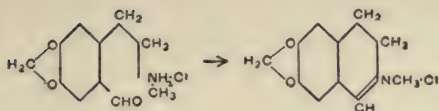
which would give for its reduction product, hydrocotarnine hydrochloride,
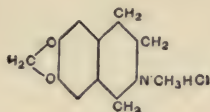
and now, since narcotine yields opianic acid and hydrocotarnine on hydrolysis and contains neither carboxyl or aldehydic groups, and also behaves as a tertiary base, it may be assumed that the union of these two complexes has occurred by elimination of water from the points marked * below :—

or
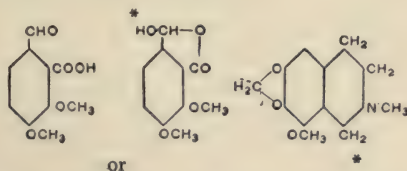
which leads to the following structure for the alkaloid :—
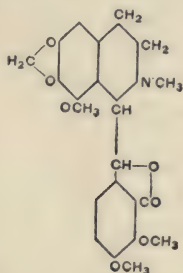
Morphine Sub-Group.—This sub-group contains morphine,

11

$C_{17}H_{19}O_3N$; codeine, $C_{18}H_{21}O_3N$; thebaine, $C_{19}H_{21}O_3N$, and pseudomorphine $(C_{17}H_{18}O_3N)_2$.

Morphine was first isolated by Serturner in the early part of the nineteenth century, and was the first basic compound obtained from the plant kingdom. It crystallizes in prisms which melt at about 247° C. Its solutions are lævo-rotatory. It behaves as a tertiary base, and contains two hydroxyl groups, one of which is phenolic, the other being alcoholic in character. It is a powerful reducing agent. Acids convert morphine into apomorphine, $C_{17}H_{17}O_2N$, by elimination of water, and also effect condensation to more complicated derivatives. *Codeine* is the methyl ether of morphine. It is also a tertiary base, its solutions being lævo-rotatory. It contains one hydroxyl group. Although mild oxidizing agents convert morphine into pseudomorphine, an analogous reaction does not take place with codeine, the reason being that the formation of pseudomorphine from morphine is due to the presence of the free phenolic hydroxyl group there present, such a state not occurring in codeine where the phenolic hydroxyl group is methylated. Phosphorus tribromide converts codeine into bromocodeine, $C_{17}H_{17}O(OCH_3).NBr.$, which, when warmed with water, is transformed into isocodeine hydrobromide, $C_{17}H_{18}O_2(OCH_3).N.HBr$. The close relationship existing between morphine and codeine was shown by Grimaux, who converted morphine into codeine by direct methylation with methyl iodide and caustic alkali, and by Matthiessen and Wright, who, by the action of concentrated hydrochloric acid at 100° C. on codeine, obtained a derivative they called chloro-codide, and which on heating with hydrochloric acid to 150° C. decomposed into methyl chloride and apomorphine.

$$C_{18}H_{21}O_3N \rightarrow C_{18}H_{20}O_2NCl \rightarrow C_{17}H_{17}O_2N + CH_3Cl.$$
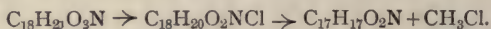
Thus both morphine and codeine contain the complex $C_{17}H_{17}ON-$, and the structure of this group has been investigated chiefly by Vongerichten, Knorr, and Pschorr. One of the earliest observations made was, that on distillation of morphine over zinc dust, phenanthrene is obtained, a result leading to the conclusion that morphine is a derivative of phenanthrene. Further

confirmation must, however, be sought, for pyrogenetic processes
such as the above are not reliable operations from which to draw
conclusions, owing to the tendency to molecular rearrangement
that frequently takes place in such processes. Such confirmation
is, however, obtained in the destructive methylation of codeine,
the methyl hydroxide of which on distillation yields methyl-
morphimethine, which in its turn, when heated with acetic
anhydride, is decomposed into methyldihydroxyphenanthrene
and dimethylhydroxyethylamine,

$$HO(CH_3O)C_{17}H_{17}O : N(CH_3)OH \rightarrow HO(CH_3O)C_{17}H_{16}O:N.CH_3 \rightarrow$$

Methyl morphimethine

$$HO(CH_3O)C_{14}H_8 + HO.C_2H_4.N(CH_3)_2$$
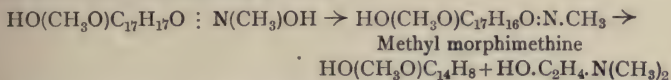
The phenanthrene derivative is phenolic, the parent dihydroxy-
phenanthrene being known as *morphol*, oxidation of the acetyl
derivative yielding dihydroxyphenanthrene quinone [in the form
of its diacetyl derivative], which, since it contains the hydroxyl
groups intact, shows that they are not attached to the adjacent
carbon atoms of the $C_{14}H_{10}$ nucleus. Again, that they are both
contained in one ring is shown by the fact that potassium
permanganate oxidizes the quinone to phthalic acid, thus
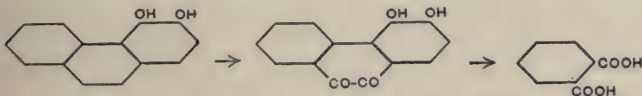
The two hydroxyl groups are shown to be in the ortho-position,
since an alkali fusion of morphine yields protocatechuic acid,
and by the behaviour of morphol to mordanted fibre, towards
which it acts as an alizarine. Further confirmation is met with
in the synthesis of dihydroxyphenanthrene and its derivatives as
follows. 3-Hydroxyphenanthrene quinone may be directly con-
verted into morphol quinone by nitration, reduction of the nitro-
compound, diazotization of the amino-quinone and subsequent
boiling with water, this series of reactions being the first direct
synthesis of a morphine decomposition product directly from
phenanthrene. Again, in 1900, Pschorr, by the following series
of reactions, prepared 3.4-dimethoxyphenanthrene identical with
the dimethyl morphol previously obtained by Vongerichten from

methyl morphol, which in its turn was prepared from codeine. The Perkin condensation of o-nitrovanillin methyl ether and sodium phenylacetate yields a-phenyl-2-nitro-3.4-dimethoxy cinnamic acid. This acid is reduced to the amino-acid which is then diazotized, and the solution of the diazo-compound in sulphuric acid (in the presence of copper powder) loses nitrogen, and is converted into 3.4-dimethoxyphenanthrene-9-carboxylic acid. On distillation, the acid decomposes into 3.4-dimethoxyphenanthrene (dimethyl morphol) and carbon dioxide.
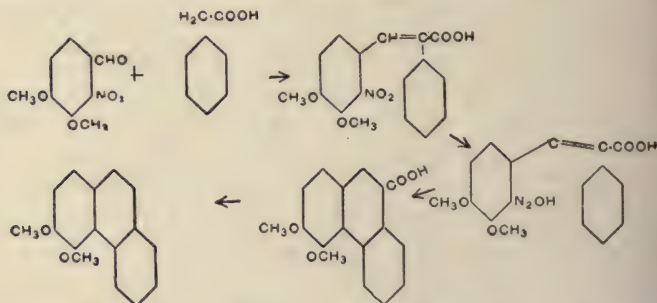
By a similar set of reactions starting out from o-nitroacetyl-isovanillin, 3-methoxy-4-acetoxyphenanthrene-9-carboxylic acid is formed. Oxidation of this acid yields the corresponding phenanthrene-quinone,
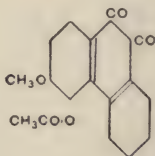
identical with acetyl-methylmorphol quinone, showing thus that methyl morphol is 3-methoxy-4-hydroxyphenanthrene.

Methylmorphimethine on treatment with acetic anhydride is converted into a stereo-isomer, from which by destructive methylation and distillation of the methyl hydroxide, methyl morphenol is obtained, the latter substance when heated with hydriodic acid passing into *morphenol*, $C_{14}H_7O(OH)$,

$$C_{17}H_{16}O(OH)(OCH_3):NCH_3 \rightarrow C_{17}H_{16}O(OH)(OCH_3):N(CH_3)_2I \rightarrow$$
$$C_{17}H_{16}O(OH)(OCH_3):N(CH_3)_2.OH$$

$$HO.C_{14}H_7O \quad \leftarrow \quad (CH_3O).C_{14}H_7O + N(CH_3)_3 + 2H_2O + C_2H_4$$
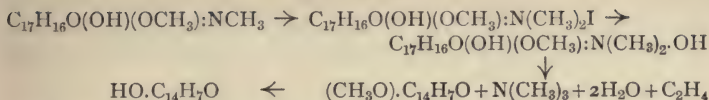
and since morphenol readily passes into morphol on reduction it is most probably to be represented as

The base, $C_4H_{11}ON$, was shown by Knorr to be identical with one previously prepared by Ladenburg from dimethylamine and ethylene chlorhydrin, and is thus a hydroxyethyldimethylamine (ethanol-dimethylamine) $HO.CH_2.CH_2.N(CH_3)_2$. This result led Knorr to conclude that morphine contained an oxazine ring, and the parent base corresponding to this ring system was designated as *morpholine*.
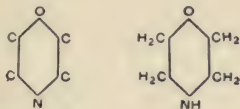
Oxazine ring

Now codeine, on oxidation, yields a ketone *codeinone*, $C_{18}H_{19}O_3N$, and this ketone, on heating with acetic anhydride, is decomposed into 3-methoxy-4.6-dihydroxyphenanthrene and hydroxyethyl-dimethylamine, which indicates also that codeine is a derivative of 3.4.6-trihydroxyphenanthrene. In his later work Knorr has come to the conclusion that the oxazine ring in all probability does not exist in the pre-formed state in these alkaloids, since the synthetic phenol ethers of ethanol-dimethylamine and of methyl morphol do not behave like α-methylmorphimethine towards sodium ethoxide, the assumption of an oxazine ring requiring these ethers and the methine base to have the same constitution and to behave in a similar fashion; and again, Freund's results, obtained from the action of magnesium phenyl bromide on thebaine, suggest that a "bridge" oxygen atom has taken part in the reaction. Further, from an examination of the

decomposition products of morphine, codeine, and thebaine, it is concluded that all three are derivatives of 3.6-dihydroxy-phenanthrylene oxide
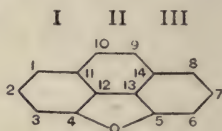
and the following conclusions are deduced. The hydroxyl group at 3 is phenolic, whilst that at 6 is alcoholic in character, the oxygen linking between 4 and 5 being indifferent. The group $CH_2.CH_2.N.CH_3$ is attached to the phenanthrene nucleus as a side ring ether at 9 or 10, this result being arrived at by comparison of the alkaloids of the group with papaverine. Again, the ring (II) is a dihydrobenzene ring containing two extra hydrogen atoms at 9 and 10, whilst (III) is a tetrahydrobenzene ring. Thus finally Knorr suggests for morphine the constitution
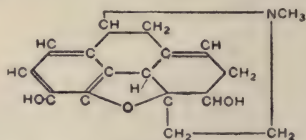
The position of attachment of the side chain is shown as follows. The decomposition of α-methylmorphimethine shows that it must be attached to ring (III). Again, codeinone methiodide decomposes, when heated with alcohol to 150° C., into dimethylamino-methyl ether and 4.6-dihydroxy-3-methoxyphenanthrene, whilst in a similar manner ψ-codeinone obtained from ψ-codeine yields the same ether and 4.8-dihydroxy-3-methoxyphenanthrene, so that ψ-codeine must contain its carbonyl group at position 6 and codeine at position 8, and hence in the conversion of codeine into ψ-codeine the hydroxyl group must migrate from 6 to 8, and since both codeine and ψ-codeine yield the same desoxycodeine, the place of attachment of the side ring must remain intact during the migration of the hydroxyl group, so that the side chain cannot be attached to position 8. Position 6 is excluded, since codeinone

has its carbonyl group there, and similarly position 7 is excluded, since the Claisen reaction shows that codeinone contains the grouping $-CH_2.CO-$, so that position 5 alone remains for the point of attachment of the $-CH_2\text{-}CH_2\text{-}N-$ chain. Positions 13 and 14 are excluded, because the side chain is found attached to ring (III) even in thebenine, which is completely aromatic in character. The double bond between 8 and 14 is shown by the ketonic character of hydroxymethylmorphimethine, which is produced when hydroxycodeine is boiled with an aqueous solution of sodium hydroxide, and since hydroxycodeine, on oxidation with chromic acid, yields Vongerichten's acetylmethylmorphol quinone (see above), it follows that hydroxycodeine must contain its alcoholic hydroxyl group at 9 or 10. Hence hydroxymethylmorphimethine must be
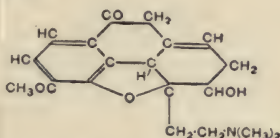
Hence, if morphine is to be represented as above, which seems highly probable in the light of Knorr's work, codeine is the 3-methyl ether of morphine.

Thebaine, $C_{19}H_{21}O_3N$, is a tertiary base which contains no hydroxyl groups, but, on the other hand, possesses two methoxy groups. The relationship existing between morphine, codeine, and thebaine may be represented by the following formulæ :—

$$HO.C_{15}H_{14}ON \begin{bmatrix} -CHOH \\ | \\ -CH_2 \end{bmatrix} \qquad CH_3O.C_{15}H_{14}ON \begin{bmatrix} -CHOH \\ | \\ -CH_2 \end{bmatrix}$$

$$CH_3O.C_{15}H_{14}ON \begin{bmatrix} -CO \\ | \\ -CH_2 \end{bmatrix} \qquad CH_3O.C_{15}H_{14}ON \begin{bmatrix} -COCH_3 \\ \| \\ -CH \end{bmatrix}$$
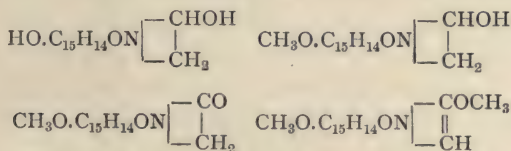
since Knorr found that thebaine, on hydrolysis with dilute sulphuric acid, yields a certain amount of codeinone, whilst Freund, by the action of bromine on thebaine, obtained an additive product which spontaneously decomposed into methyl

bromide and bromocodeinone. Thus thebaine appears as the methyl ether of the enolic form of codeinone.

Among the various decomposition products of thebaine that have been investigated are *thebenine*, $C_{18}H_{19}O_3N$ [which is formed by the action of dilute hydrochloric acid on the alkaloid, one methoxy group being hydrolyzed], and *thebaol*, $C_{16}H_{14}O_3$. The methyl ether of thebenine (methebenine) has been shown by Pschorr to be phenolic in character, so that the third oxygen atom (which is not accounted for by the methoxy groups), is therefore phenolic, and not part of a furan ring. The hydroxyl group in methebenine cannot be methylated until the secondary nitrogen atom has been converted into a quaternary nitrogen atom, and the resulting salt, when heated with the alkaline hydroxides, yields trimethylamine and an unsaturated phenanthrene derivative, which may be oxidized to trimethoxyphenanthrene tricarboxylic acid. Thus all three oxygen atoms in methebenine are linked directly to the phenanthrene nucleus, and it probably is to be represented as

$$C_{14}H_6(OCH_3)_2 . OH[CH(CH_3) . NHCH_3].$$
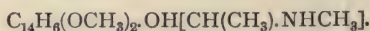
The above reactions could be thus represented

$$\text{Thebenine} \qquad\qquad \text{Methebenine}$$
$$HO . C_{16}H_{11}O(OCH_3) . NHCH_3 \;\rightarrow\; HO . C_{16}H_{10}(OCH_3)_2 . NHCH_3$$
$$\downarrow$$
$$C_{16}H_{10}(OCH_3)_3 . N(CH_3)_3I$$
$$\downarrow$$
$$C_{16}H_{10}(OCH_3)_3 . N(CH_3)_3 . OH ;$$
$$C_{14}H_6(OCH_3)_3 . COOH \;\leftarrow\; N(CH_3)_3 + H_2O + C_{14}H_6(OCH_3)_3CH : CH_2$$
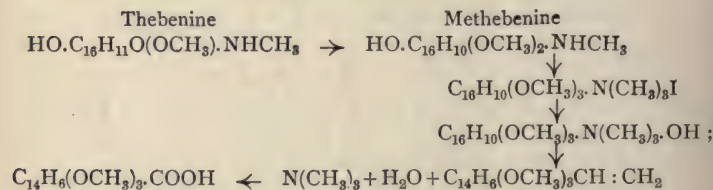
thus showing the relation of thebaine to phenanthrene. Again, thebaine methiodide, when warmed with sodium ethoxide, yields tetramethyl ethylene diamine, and the non-nitrogenous *thebaol*, $C_{16}H_{14}O_3$, the diamine resulting probably from the decomposition of an intermediately formed dimethylvinylamine and a small quantity of dimethylamine which is also produced.

$$C_{19}H_{21}O_3N . CH_3I \;\longrightarrow\; C_{16}H_{14}O_3 + [CH_2 : CH . N(CH_3)_2] + HI.$$
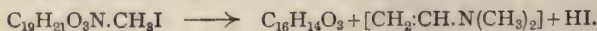
Thebaol is also formed when thebaine methyl iodide is warmed with acetic anhydride in the presence of silver acetate. Thebaine

alone on treatment with acetic anhydride yields acetyl thebaol and methyl hydroxyethylamine.

$$(CH_3O)_2.C_{16}H_{12}ONCH_3 + H_2O =$$
$$(CH_3O)_2.C_{14}H_7O.COCH_3 + HO.CH_2.CH_2.NHCH_3.$$
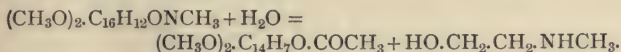
Thus thebaol is derived from a compound containing three hydroxyl groups, and since on distillation over zinc dust it yields phenanthrene it is probably a trihydroxyphenanthrene derivative. This latter conclusion receives proof by the following series of reactions. Chromic acid oxidizes thebaol to thebaol quinone $(CH_3O)_2.C_{14}H_5O_2.OH$, which, by further oxidation with potassium permanganate, is converted into o-methoxyphthalic acid, a result indicating that the two methoxy groups are not present in one and the same ring; thebaol quinone has been synthesized by Pschorr by condensing *vic*-(o)nitroisovanillin with *p*-methoxyphenyl acetic acid, the resulting nitro-cinnamic acid derivative being then reduced to the amino-acid and diazotized. The diazo compound when boiled in alkaline solution is converted into 4-hydroxy-3.6-dimethoxyphenanthrene-9-carboxylic acid, the acetyl derivative of which oxidizes directly to acetyl thebaol quinone, so that thebaol is a derivative of 4-hydroxy-3.6-dimethoxyphenanthrene.
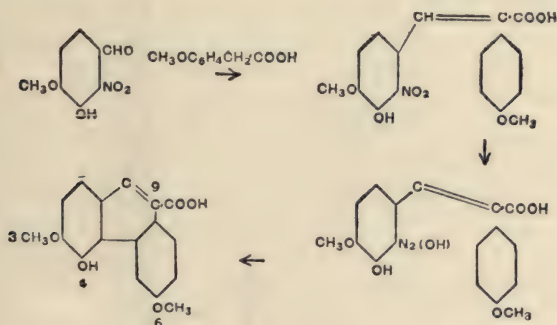
Similarly by the condensation of *vic*-(o)-nitrovanillin methyl ether and *p*-methoxyphenyl acetic acid, methyl thebaol is formed.
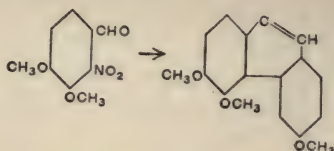
Thus thebaine contains the same type of grouping as morphine and codeine, and can also be converted into codeinone, so that the conclusion that it is the methyl ether of the enolic form of codeinone seems justified. For the sake of convenience of reference, the chief decomposition products of these three alkaloids are shown in the following chart.

Hydrastine, $C_{21}H_{21}O_6N$, is found in the root of the golden seal (*Hydrastis canadensis*). It crystallizes in prisms which melt at $132°$ C., and behaves as a tertiary base. In neutral solutions it is lævo-rotatory, in acid solution dextro-rotatory. It contains two methoxy groups. The constitution of this alkaloid has been determined chiefly by the investigations of Freund and his pupils in the following manner. On oxidation with a somewhat diluted nitric acid it yields opianic acid and hydrastinine, $C_{11}H_{13}O_3N$,

$$C_{21}H_{21}O_6N + H_2O + O = C_{10}H_{10}O_5 + C_{11}H_{13}O_3N,$$
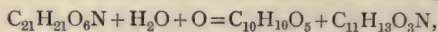
from which Freund concludes that it is a meconyl-hydrohydrastinine. Now, since hydrastinine, on heating for a short time with a concentrated solution of potassium hydroxide, is converted into a mixture of hydrohydrastinine and oxyhydrastinine,

$$2C_{11}H_{13}O_3N = \underset{\text{Hydrohydrastinine}}{C_{11}H_{13}O_2N} + \underset{\text{Oxyhydrastinine}}{C_{11}H_{11}O_3N} + H_2O$$
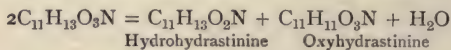
a reaction resembling Cannizzaro's, in that it consists of a simultaneous oxidation and reduction process, it seems that hydrastinine must be regarded as an aldehyde, $C_{10}H_{12}NO_2$, whilst hydrohydrastinine and oxyhydrastinine are the internal anhydrides of the corresponding alcohol and acid. Further confirmation of the aldehyde character of hydrastinine is given by the fact that it forms an oxime. It also possesses the character of a secondary base, and contains a methyl group attached to the nitrogen atom. On oxidation with potassium permanganate, hydrastinine is converted into hydrastinic acid, $C_{11}H_9O_6N$, which, by further oxida-

Phe

Zn d

MORPHINE ($_3$COOH + $C_{14}H_8(OAc)_2$

CH$_3$I |

$\downarrow$
Morphol
$C_{14}H_3(OH)_2$

$\longrightarrow C_{14}H_6O_2(OCH_3)OCOCH_3$
Acetyl methyl morphol quinone
(synthesized by Pschorr)

CODEINE C_1
C_1CH$_2$.CH$_2$N(CH$_3$)$_2$
synthesized)

$\searrow$ O

Ac$_2$
$C_{18}H_{19}O_3N$ $\rightarrow$
Code none

$\uparrow$

THEBAINE (H_3)$_3$ + H_2O + $C_{14}H_6(OCH_3)_3$.CH : CH$_2$
$\downarrow$ O
$C_{14}H_6(OCH_3)_3$.COOH
or

$\downarrow$
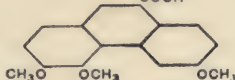
(CH$_3$O $\longrightarrow$ Thebaol quinone
(synthesized by Pschorr)

HO.C

baine,
rd the

tion with nitric acid is transformed into what must be regarded as the methyl imide of hydrastic acid, $C_{10}H_7O_4N$,

$$C_{11}H_9O_6N + O = C_{10}H_7O_4N + CO_2 + H_2O$$
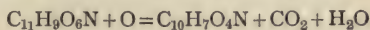
for, on hydrolysis, the latter compound is decomposed into methylamine and the dibasic hydrastic acid $C_7H_4O_2(COOH)_2$.

$$C_{10}H_7O_4N + 2H_2O = CH_3NH_2 + C_7H_4O_2(COOH)_2.$$
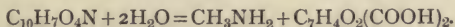
Hydrastic acid contains its carboxyl groups in the ortho-position to each other, since it forms an anhydride and an imide, and on treatment with phosphorus pentachloride yields an acid chloride, which, when boiled with water, is converted into a dihydroxyphthalic acid,

$$C_7H_4O_2(COOH)_2 \xrightarrow{PCl_5} C_7H_2Cl_2O_2(COCl_2)$$
$$\downarrow 4H_2O$$
$$CO_2 + 4HCl + (HO)_2.C_6H_2(COOH)_2$$
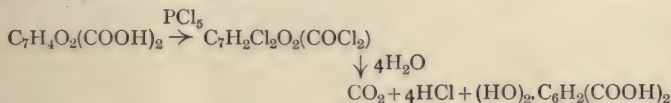
identical with the dihydroxyphthalic acid obtained by Rossin on heating metahemipinic acid with hydriodic acid, therefore represented as
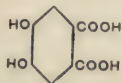
Thus hydrastic acid would appear to be the methylene ether of 4.5-dihydroxyphthalic acid.
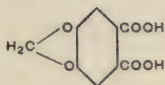
Further confirmation of this structure is given by the fact that fuming nitric acid converts it into the methylene ether of dinitro-pyrocatechin, which has also been obtained by the action of fuming nitric acid on piperonylic acid.

Hydrastic acid   Piperonylic acid
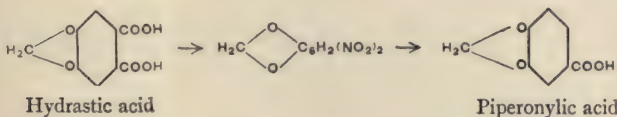
Consequently the easiest way of formulating hydrastinic acid in order to show its conversion into the methyl imide of hydrastic acid on oxidation will be
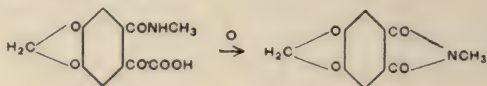
and the production of this hydrastinic acid by the oxidation of oxyhydrastinine will be explained if the latter is written as
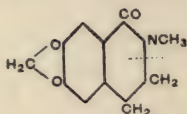
thus leading to the following formulæ for hydrohydrastinine and hydrastinine.

Hydrohydrastinine   Hydrastinine
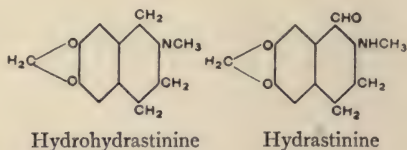
Since hydrastine decomposes on oxidation into opianic acid and hydrastinine, the connection between these two portions in the molecule must be effected by the carbon atoms from which the aldehyde groups of the opianic acid and hydrastinine are obtained, and consequently the alkaloid must be represented by the annexed formula.
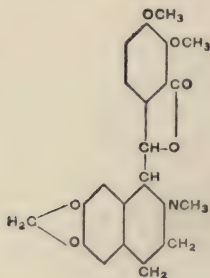
The constitution for hydrastinine, given above, has received further confirmation by its synthesis at the hands of Fritsch, as follows. Piperonal condenses with amido-acetal to form piperonal acetalamine, which, on treatment with sulphuric acid, is transformed into Bz-2.3-methylenedihydroxyisoquinoline. The methiodide of the latter compound on reduction is converted into methylene dihydroxy-methyl-tetrahydroisoquinoline or hydrohydrastinine, and this compound on oxidation with potassium bichromate and sulphuric acid passes into hydrastinine.
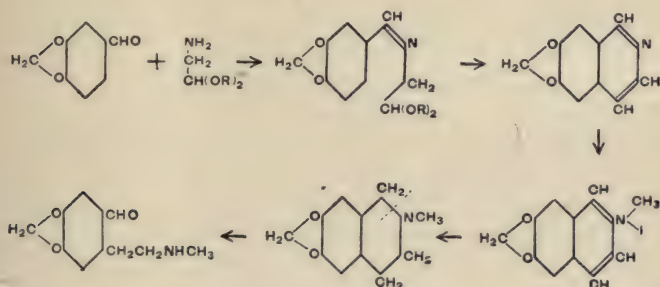
Berberine, $C_{20}H_{17}O_4N$, is found widely distributed in the vegetable kingdom. It crystallizes in yellow prisms which contain a variable amount of water of crystallization, and in the anhydrous condition melts at 120° C. It behaves as a weak tertiary base and contains two methoxy groups. The earlier investigations as to the constitution of berberine give very little insight as to its structure, the chief facts observed being that alkaline potassium permanganate oxidizes it to hemipinic and hydrastic acids, whilst concentrated nitric acid oxidizes it to berberonic acid, $C_5H_2N(COOH)_3(\alpha\gamma\beta^1)$, results pointing to the presence of a pyridine ring and two benzene rings in the molecule. Our knowledge of the method by which these ring systems are linked together is due to the researches of W. H. Perkin, jun., on the products of oxidation of the alkaloid by potassium permanganate. Perkin found that beside hemipinic and hydrastic acids, the following six oxidation products were formed :—

Oxyberberine	.	.	$C_{20}H_{17}O_5N$
Dioxyberberine	.	.	$C_{20}H_{17}O_6N$
Berberal	.	.	$C_{20}H_{17}O_7N$
Anhydroberberilic acid		.	$C_{20}H_{17}O_8N$
Berberilic acid	.	.	$C_{20}H_{19}O_9N$
Berilic acid	.	.	$C_{20}H_{15}O_8N$

and of these the two that throw most light on the constitution of the alkaloid are berberilic acid and berberal. Berberilic acid is a dibasic acid, which, when heated above 170° C., passes into the monobasic anhydroberberilic acid, an internal anhydride of berberilic acid, and also a free acid, since under certain conditions it can form salts, and also an acid chloride, amide, and anilide. When berberilic acid is boiled with dilute sulphuric acid, it is decomposed into hemipinic acid, and a base of composition, $C_{10}H_{11}O_4N$. The latter, when heated to 180° C., loses a molecule of water and forms an internal anhydride, $C_{10}H_9O_3N$. The nitroso-derivative of this anhydride on hydrolysis with caustic alkali loses nitrogen, and is transformed into a monobasic acid, $C_{10}H_{10}O_5$, which, on heating, again yields an internal anhydride, $C_{10}H_8O_4$. No further results were obtained by the oxidation of this anhydride, but it was found that if it were heated under pressure to 170° C. with hydrochloric acid, it decomposed with elimination of carbon and formation of a substance of composition $C_9H_8O_4$. This decomposition product gave an intense catechol reaction on the addition of ferric chloride, and also reduced Fehling's solution and warm ammoniacal solutions of silver nitrate. It also gave a white precipitate on the addition of lead acetate. These reactions and decompositions indicate the presence of piperonyl derivatives, and consequently the above series of compounds can be formulated as follows :—

$C_{10}H_{11}NO_4$ $C_{10}H_9NO_3$ $C_{10}H_8(NO).NO_3.$

ω-aminoethylpiperonylcarboxylic acid

$C_9H_8O_4$ $C_{10}H_8O_4$ $C_{10}H_{10}O_5$
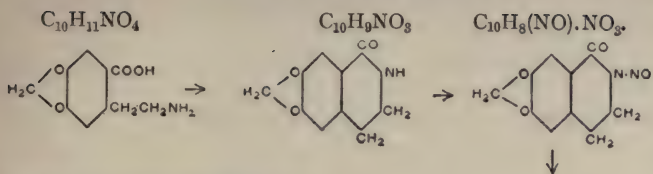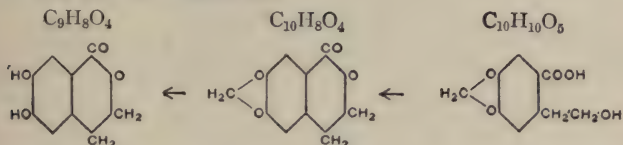
It will be noticed that the compound $C_{10}H_9O_3N$ closely resembles oxyhydrastinine, from which it differs in composition by the presence of the group $>NH$ instead of $>N.CH_3$, and for this reason Perkin called it noroxyhydrastinine. It was converted into oxyhydrastinine by the following series of reactions. The nitrosamine, $C_{10}H_8(NO)NO_3$ (see above), on heating with caustic soda, is decomposed into nitrogen, and the acid, $C_{10}H_{10}O_5$ (ω-hydroxyethylpiperonylic acid), the anhydride of the latter by the action of phosphorus pentachloride, yielding a compound, $C_{10}H_8O_3Cl_2$, which is readily hydrolyzed to the acid, $C_{10}H_9O_4Cl$ (ω-chloroethylpiperonylic acid). The methyl ester of this acid is then heated with an alcoholic solution of methylamine to 130° C., and the product obtained warmed with alcoholic potash, when methyl alcohol is split off and oxyhydrastinine is formed.
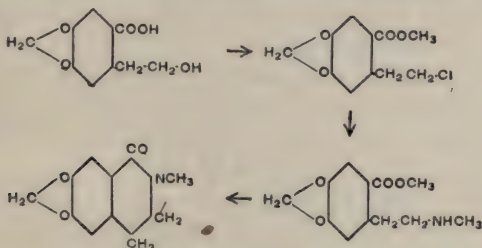
This series of reactions thus shows the close relation existing

between berberine and hydrastine, and also that berberine may be considered as a derivative of isoquinoline.

Since berberilic acid on hydroylsis yields hemipinic acid, and ω-aminoethylpiperonyl carboxylic acid, it must be
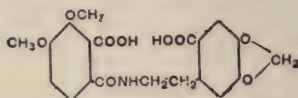
which consequently gives for anhydroberberilic acid,
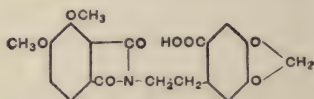
a conclusion shown to be correct since, on evaporation of aqueous solutions of hemipinic acid and ω-aminoethylpiperonylic acid, a hemipinate of the acid is formed, which passes into anhydroberberilic acid when heated.

$$(CH_3O)_2.C_6H_2(COOH).COO.NH_3.CH_2.CH_2(HOOC).C_6H_2(O_2CH_2)$$
$$\downarrow$$
$$2H_2O + (CH_3O)_2C_6H_2(CO)_2:N.CH_2.CH_2.(HOOC).C_6H_2(O_2CH_2)$$
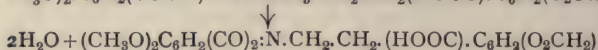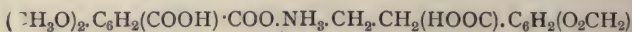
Berberal, $C_{20}H_{17}O_7N$, crystallizes in plates, which melt at 150° C.; it possesses aldehydic properties, and on hydrolysis is decomposed with formation of ψ-opianic acid and noroxyhydrastinine.

$$C_{20}H_{17}O_7N + H_2O = C_{10}H_{10}O_5 + C_{10}H_9O_3N$$
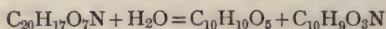
The ψ-opianic so obtained possesses the properties of an orthoaldehydo acid, is monobasic, and contains two methoxy groups. When fused with caustic potash it yields protocatechuic acid. Its oxime when heated is converted into hemipinimide. On reduction with sodium amalgam the acid is converted into ψ-meconine, which thus, taken in conjunction with the other reactions, leads to the following structural formula for the acid :—

ψ-opianic   ψ-meconine   Hemipinimide
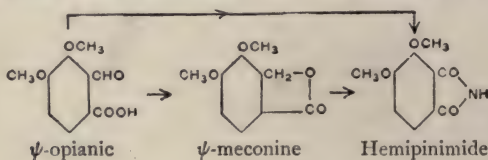
Now opianic acid condenses with ω-aminoethylpiperonylic anhydride to form isoberberal, $C_{20}H_{17}O_7N$, which has properties exactly similar to berberal; and Liebermann has shown that when opianic acid reacts with aniline in the cold, an anilino-opianic acid is formed, the opianic acid reacting in the tautomeric hydroxyphthalide form.
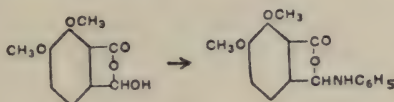
From a study of this and similar reactions it seems clear that in the condensations of opianic acids with bases it is always the carbon atom of the aldehyde group which is attached to the nitrogen atom in the final product, and in this way the formation of isoberberal may be represented by the following scheme.
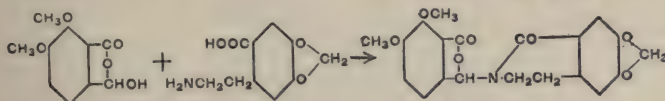
Again, since ψ-opianic acid is very similar in structure and in its reactions to opianic acid, it may be assumed that it will condense with basic substances in an exactly similar manner to opianic acid, and as ψ-opianic acid and ω-aminoethyl piperonylic anhydride condense to form berberal this reaction must take place as follows :—
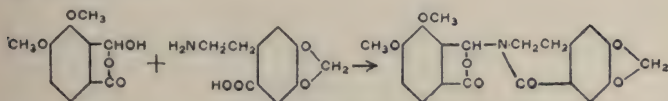
which, of course, establishes the structure of berberal.

Perkin points out that the condensations shown above are probably not so simple as suggested by Liebermann, since, in the formation of berberal and isoberberal, the first stage in the process is the formation of the salt of the acid with the base,

12

thus from ψ-opianic anhydride and ω-aminoethylpiperonyl anhydride, the salt
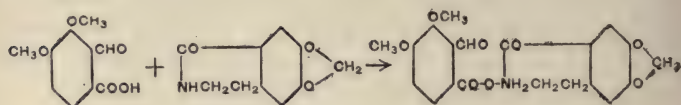
is produced, and when heated to 180° C. is transformed into berberal, aldol formation probably taking place, followed by rearrangement.
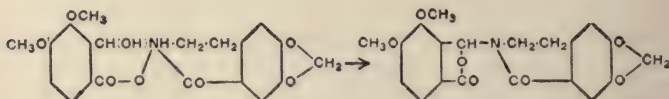
Thus, knowing the constitutional formulæ of berberilic acid and berberal, it is evident that the alkaloid must contain the groupings
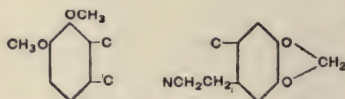
and as the position of the methoxy groups is determined by the facts mentioned above, the simplest structure that can be given to the alkaloid in order to explain its properties and decompositions is
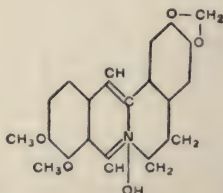
The oxidation to berberal can then be explained by the following scheme :—
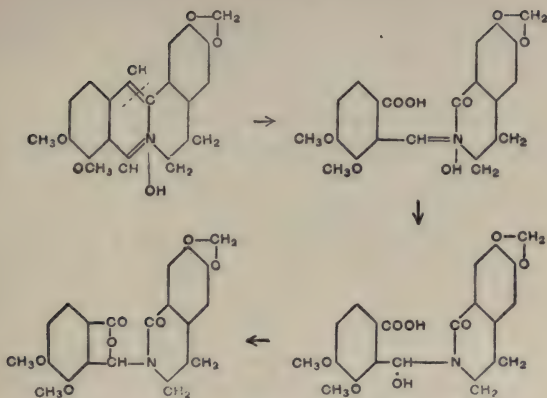
The salts of berberine are derived from the hydroxylic formula given above, but the alkaloid probably itself exists in the corresponding aldehydic modification. Gadamer, from the action of barium hydroxide on a solution of berberine sulphate, obtained a brownish red strongly alkaline solution, which, on the addition of excess of sodium hydroxide, gave a modification of berberine, insoluble in water, faintly alkaline, and also aldehydic in character. This form he named *berberinal*. It forms an oxime, reacts with magnesium alkyl iodides to form homologues of berberine, and undergoes the Cannizzaro reaction. On the above formulation of berberine it would be represented as
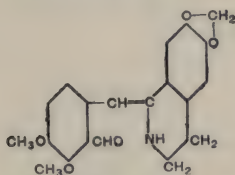
which brings it into line with the formula given for hydrastine (p. 172).

All doubts as to the constitution of berberine may now be considered as settled, since the alkaloid has recently been synthesized by Pictet.

In this synthesis, homoveratryl chloride is condensed with

homopiperonylamine, and the resulting anilido-compound when heated in xylene solution with phosphorus pentoxide is converted into veratryl-methylene dioxy-dihydroisoquinoline. The isoquinoline compound so formed is then reduced with tin and hydrochloric acid, and the reduction product condensed with methylal, when tetrahydro-berberine is formed. Oxidation of tetrahydroberberine with dilute nitric acid then yields berberine nitrate, identical with that obtained from the alkaloid itself. The stages in the reaction are shown in the following diagram :–
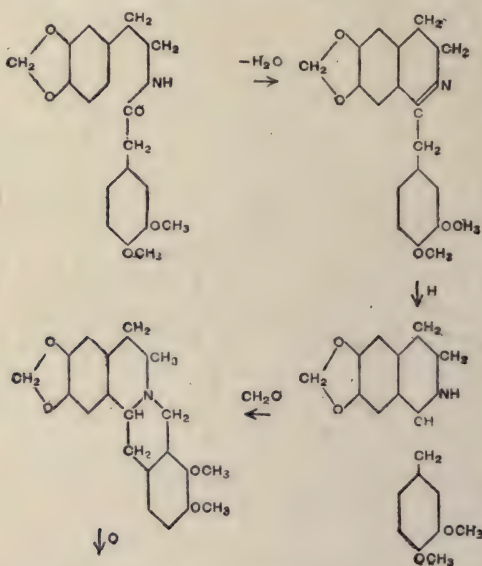
Berberine

Corydaline, $C_{22}H_{27}O_4N$, is the chief alkaloidal constituent of the root of Corydalis cava. Its solutions are alkaline, possess a bitter taste, and are dextro-rotatory. The action of concentrated hydriodic acid on the alkaloid shows that it contains four methoxy groups. It does not contain a methyl group attached to nitrogen. It has the properties of a tertiary base. For our knowledge of

the constitution of corydaline we are indebted to the researches of Dobbie and Lauder, who showed that on oxidation with a hot solution of potassium permanganate, hemipinic acid and meta-hemipinic acid were formed, this result pointing to the presence of two benzene rings in the nucleus. At the same time a nitrogen containing product *corydaldine*, $C_{11}H_{13}O_3N$, was obtained, and it may be assumed that an isoquinoline nucleus is present, since the oxidation of corydaldine yields metahemipinic acid.

Mild oxidants, such as nitric acid, or an alcoholic solution of iodine, convert corydaline into dehydrocorydaline, $C_{22}H_{23}O_4N$, which may be further oxidized to the dibasic corydic acid $C_{18}H_{17}O_6N$. This acid in its turn may be oxidized by potassium permanganate into a tribasic acid, corydilic acid $C_{17}H_{15}O_8$, meta-hemipinic acid, and α-methyl pyridine tricarboxylic acid, which is either
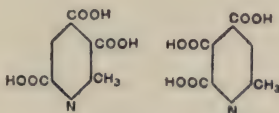
since further oxidation converts it into pyridine 2.3.4.6-tetra-carboxylic acid. These results point to corydilic acid possessing the following structure :—
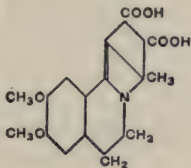
As corydilic acid is formed by the oxidation of dehydrocory-daline, the two carboxyl groups probably result from the destruction of another ring containing two methoxy groups, since dehydrocorydaline, like corydaline itself, contains four methoxy groups, so that dehydrocorydaline must be represented as
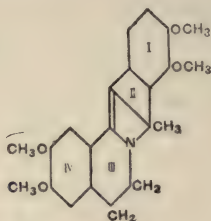
which gives for corydaline itself
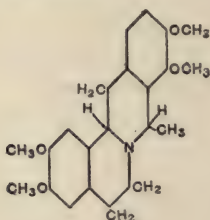
The formula for dehydrocorydaline given above accounts quite well for the various oxidation products obtained from it, corydic acid being formed by the destruction of ring (I), and corydilic acid from this by the destruction of ring (III).

Corydaldine closely resembles noroxyhydrastinine, from which it only differs by the carbon and hydrogen content CH_4, and since corydaldine contains two methoxy groups, whilst noroxyhydrastinine has not any, it would seem that the difference is to be ascribed to the grouping

$$CH_3O.C— \atop CH_3O.C—$$ being present instead of $$O—C— \atop CH_2 \atop O—C—$$
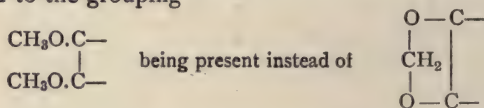
Corydaldine shows a very remarkable likeness to berberine in that it yields decomposition products very similar to those obtained from ω-aminoethylpiperonyl carboxylic acid, thus it forms a nitroso-derivative, which, when warmed with solutions of the caustic alkalies, is transformed into the sodium salt of ω-hydroxyethyl veratric acid, nitrogen being eliminated during

the progress of the reaction. The free acid on liberation from its solution loses water and passes into its anhydride, which contains two methoxy groups, since on oxidation with potassium permanganate it is converted into metahemipinic acid. A further argument in favour of its constitution is given by the fact that on heating with hydrochloric acid it yields ω-hydroxyethyl catechol carboxylic anhydride identical with that obtained by Perkin from berberine. These reactions may be illustrated in the following way :—
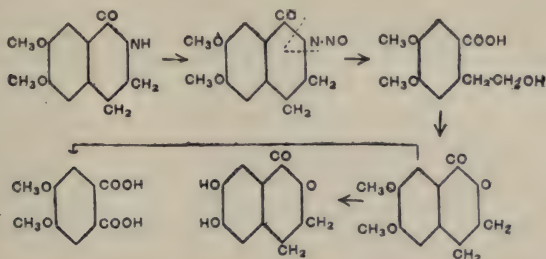
Thus the presence of the isoquinoline nucleus may be considered as definitely determined. Again, the formation of hemipinic acid by the oxidation of the above anhydride shows that hemipinic acid is derived from the benzene ring of the isoquinoline complex, hence the ring, destroyed when corydaline is oxidized by dilute nitric acid, is the ring which yields hemipinic acid when the alkaloid is oxidized by potassium permanganate, and consequently the benzene ring and the isoquinoline ring each contain two methoxy groups.

Quinoline Group.—The principal members of this group are the alkaloids strychnine, $C_{21}H_{22}O_2N_2$, and brucine, $C_{23}H_{26}O_4N_2$, the latter apparently being the dimethoxy-derivative of the former.

Strychnine is found in nux-vomica, the seed of Strychnos nux-vomica, and in other plants of the genus Strychnos. It crystallizes in prisms which melt at 269°, and is lævo-rotatory. It is a tertiary base, and forms salts with only one equivalent of acid. It does not contain a mexthoxy-group. Many investigations

have been made in order to determine the structure of this alkaloid, but few deductions have been drawn by the earlier workers as to its constitution. The presence of an aromatic nucleus may be concluded from the fact that sulphonic acids have been obtained, whilst nitric acid and the halogens also yield substitution derivatives. Strychnine is readily oxidized, but very little light has been thrown on the structure of the molecule from a study of the oxidation products. The most important researches from which any idea as to constitution can be drawn are those of Tafel, Leuchs, and Perkin. Tafel has shown that the action of alkalis on strychnine is one of hydrolysis, a molecule of water being added, with the resulting formation of strychnic acid, $C_{21}H_{24}O_3N_2$, and isostrychnic acid, $C_{21}H_{24}O_3N_2$, this result being obtained by the use of baryta water or of sodium methoxide as hydrolyzing agents. Strychnic acid contains the groups $-COOH$ and $>NH$, the presence of the latter group being shown by the formation of a nitrosamine. It is also a tertiary base, and on treatment with methyl iodide yields methyl strychnic acid methiodide. From these results, taken in conjunction that when heated, strychnic acid reverts to strychnine, Tafel concluded that the alkaloid contained the group $\begin{array}{c} \diagup CO \\ \diagdown N, \end{array}$ the two substances being related thus :—

$$N : C_{20}H_{22}O \begin{array}{c} -CO- \\ | \\ = \ N \end{array} \gtrless \ N : C_{20}H_{22}O(COOH) : NH$$
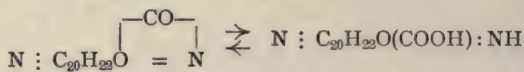
such a grouping readily explaining the fact that strychnine only combines with one equivalent of an acid, the second nitrogen atom being present in the form of the non-basic group $-CO.N:$.

The presence of this grouping receives further confirmation by a study of the reduction products of strychnine. By heating the alkaloid with hydriodic acid and phosphorus an atom of oxygen is eliminated, and a mon-acid base, $C_{21}H_{26}ON_2$ (desoxystrychnine) is formed, which, on hydrolysis with sodium ethoxide, is converted into desoxystrychnic acid, $C_{21}H_{28}O_2N_2$, an imino-acid, resembling strychnic acid in properties. Thus the groups

N : and .CO.N : of the strychnine molecule are unaltered by reduction, and the reaction may be formulated.

$$N : C_{20}H_{22}O = \overset{\overset{\displaystyle -CO-}{\vert\qquad\vert}}{N} \xrightarrow{H} N : C_{20}H_{26} = \overset{\overset{\displaystyle -CO-}{\vert\qquad\vert}}{N}$$

$$\downarrow H_2O$$

$$N : C_{20}H_{25}(COOH) : NH$$
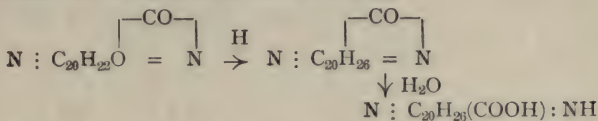
Desoxystrychnine, on reduction with sodium and amyl alcohol, is converted into strychnoline $C_{21}H_{26}N_2$ (the group $-CO-N$: becoming $-CH_2.N$:), which, on electrolytic reduction, becomes dihydrostrychnoline, $C_{21}H_{28}N_2$. The electrolytic reduction of strychnine itself yields tetrahydro-strychnine, which readily loses water and passes into strychnidine

$C_{21}H_{26}ON_2$	$\rightarrow$	$C_{21}H_{26}N_2$	$\rightarrow$	$C_{21}H_{28}N_2$
Desoxystrychnine		Strychnoline		Dihydrostrychnoline
$C_{21}H_{22}O_2N_2$	$\rightarrow$	$C_{21}H_{26}O_2N_2$	$\rightarrow$	$C_{21}H_{24}ON_2$
Strychnine				Strychnidine
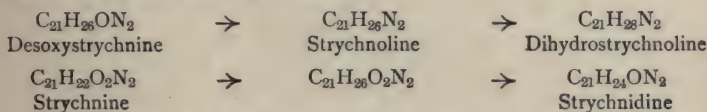
The presence of the quinoline complex in the molecule has been determined in the following way. Nitration yields picric acid and a monobasic acid, dinitrostrychol carboxylic acid $(NO_2)_2.C_9H_2N(OH)_2.COOH$. This acid, when heated to 200° C. with water, loses carbon dioxide and is transformed into dinitrostrychol $(NO_2)_2.C_9H_3N(OH)_2$, a substance which Tafel regards as dinitro-dihydroxyquinoline. Again, strychnine methiodide, on treatment with silver hydroxide, yields methyl strychnine

$$CH_3I : N : C_{21}H_{22}O_2N \rightarrow HO.CH_3 : N : C_{20}H_{22}O(COOH) : NH$$

$$\downarrow$$

$$\overset{\displaystyle O\text{———— } CO}{\underset{\displaystyle CH_3N : C_{20}H_{22}O(:NH),}{\vert\qquad\qquad\vert}}$$
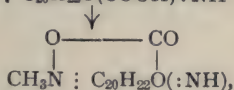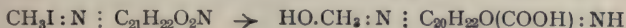
a substance showing all the properties of a betain and of a secondary base. It combines with methyl iodide to form dimethyl strychnine

$$\overset{\displaystyle O\text{——— } CO}{\underset{\displaystyle CH_3N : C_{20}H_{22}O(: NCH_3)}{\vert\qquad\qquad\vert}}$$
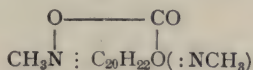
which behaves as a tertiary base, yields a nitrosamine, condenses with benzaldehyde to form a leuco-base resembling leuco-malachite green, and combines with diazobenzenesulphonic acid

to form a yellow dyestuff, properties which show its great resemblance to the dialkyl anilines and to N-methyltetrahydroquinoline. From this behaviour Tafel concludes that strychnine contains a quinoline nucleus, and that the $-NCH_3$ group in dimethylstrychnine, and hence the $-NH$ group in methylstrychnine and the $-N.CO-$ group in strychnine is combined by one linking direct to the benzene ring, and that the alkaloid must therefore contain the grouping
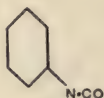
Oxidation of strychnine and of brucine (*i.e.* dimethoxystrychnine) with chromic acid gives a monobasic acid, $C_{15}H_{17}O_2N_2.COOH$, which is a carbazole derivative, since it yields carbazole when distilled over zinc dust. Again, since the oxidation of brucine yields the same acid as the oxidation of strychnine, the two methoxy-groups must have disappeared, and it follows that the benzene ring of the quinoline complex in the two alkaloids is broken down during oxidation.
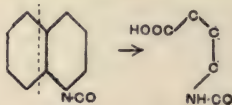
Knowing the presence of the groupings

and taking into account the number of hydrogen atoms in strychnine which point to the pyridine and carbazole nuclei being almost completely reduced, Perkin has arrived at the following conclusions concerning the structure of the molecule. As these groupings contain C_{22} and strychnine only C_{21}, at least one carbon atom is common to both. Now, since the basic nature of strychnine is due to the carbazole nitrogen atom, the

attempt to construct a formula on the assumption that one carbon atom is common to both would lead to the nitrogen atom of the carbazole residue being rendered tertiary by union with a carbon atom of the quinoline nucleus, whilst the $>CO$ group would unite with the carbazole nucleus, thus leading to a formula which cannot represent strychnine. As an alternative, it may be assumed that two carbon atoms are common to both, and that the skeleton which now contains C_{20} is completed by an additional carbon atom between the CO group and the basic nitrogen atom, thus giving
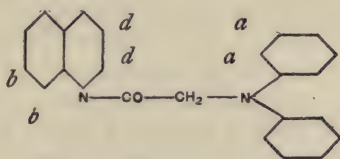
further fusion taking place between the carbon atoms at *aa* and *bb*, or *aa* and *dd*, the latter being taken as preferable, since the former would yield a seven-membered ring which would not seem likely to be formed by the elimination of water from strychnic acid, such elimination with formation of a six-membered ring being, however, quite usual. Thus the strychnine skeleton may be represented as
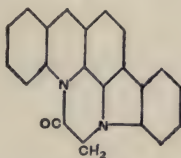
which leads to desoxystrychnine and dehydrostrychnoline being
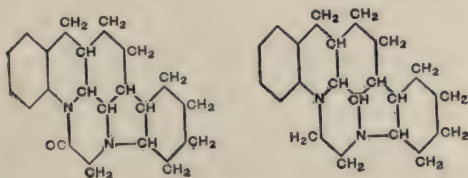
This skeletal structure also leads to an explanation of Leuchs'
investigations and to a possible formula of strychnine itself.
Leuchs found that strychnine when dissolved in acetone and
oxidized by potassium permanganate gave a dibasic acid (strych-
ninonic acid) which was ketonic in character, since it yielded
an oxime and a carbazone. This acid has the composition
$N : C_{17}H_{18}(:N.CO)(CO).(COOH)_2$. On reduction with sodium
amalgam it yields strychninolic acid, the group $> CO$ becoming
$> CH.OH$, and this alcohol acid, when left in contact with
dilute alkali for some time, is decomposed into glycollic acid
and strychninolone, $C_{19}H_{18}O_3N_2$, which has neither basic nor
acidic properties. Now to produce such a substance as strych-
ninolone it seems evident that reaction must take place between
two COOH groups and basic nitrogen atoms, and since two such
atoms are required for the process, it follows that the grouping
$:N.CO.CH_2.N:$ of the original molecule must lose $.CO.CH_2 -$,
which is therefore the source of the glycollic acid

$$:N.CO.CH_2.N: + 2H_2O = :NH + HOOC.CH_2.OH + HN:$$

thus also giving basic nitrogen atoms to react with carboxyl
groups. Hence, as the simplest way of representing the produc-
tion of strychninolone, we have the the following scheme :—
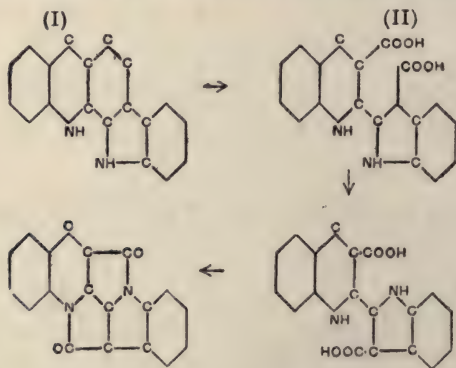
On the basis of the formulæ (I) and (II) above, the following

structural formulæ can be given to strychninonic acid and to strychnine.
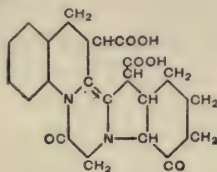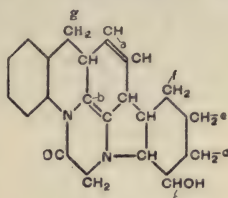
Strychninonic acid   Strychnine

The positions assigned to the double linkages shown in the above formula are based on the following considerations. If the formula assigned to strychninonic acid is correct, one must clearly be at a. Position b is chosen for another, because it must be situated in a stable part of the molecule, otherwise it would undergo oxidation during the preparation of strychninonic acid, but experience shows such groupings as

are not readily oxidized. The keto-acid (strychninonic acid) must arise from the oxidation of the $-$ CHOH group in strychnine, and this group cannot be in position g, for then strychninonic acid would be a derivative of benzoyl acetic acid. Positions e and f would make strychninonic acid a γ or δ hydroxy acid, but it shows no tendency to lactonize as such acids would. Of the other two available positions for the hydroxyl group, c was chosen preferably to d, by comparison of strychnine with quinine and other natural products in which such a group occurs.

Brucine has been shown by Leuchs to oxidize in a similar manner to bruconic acid, which may be reduced to brucinolic acid, and the latter then converted into brucinolone. Now, brucinolone on oxidation with nitric acid yields a quinone, the methoxy groups present being eliminated, and this quinone, on

reduction, is converted into a quinol. Perkin is of the opinion that under these conditions a paraquinone would result, which by comparison with strychninolone should therefore possess the structure (I). Consequently, brucine would then be represented by the configuration (II).

(I)   (II)
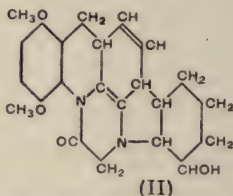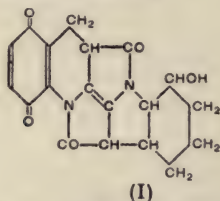
Cinchonine, $C_{19}H_{22}ON_2$, and *quinine*, $C_{20}H_{24}O_2N_2$, are found with many other alkaloids, in cinchona bark, and are very closely related, cinchonine containing an unsubstituted quinoline nucleus, whilst quinine contains a *p*-methoxy-group in the same nucleus. The cinchona bases are bitertiary and contain a hydroxyl group. Cinchonine is an unsaturated base containing the group $-CH:CH_2$ since it combines with two atoms of halogen, or with one molecule of an halogen hydride; and is instantaneously attacked by potassium permanganate in acid solution, one carbon atom being eliminated as formic acid, cinchotenine, $C_{18}H_{20}O_3N_2$, being simultaneously produced.

$$C_{19}H_{22}ON_2 + 4O = H_2CO_2 + C_{18}H_{20}O_3N_2.$$
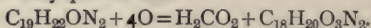
Cinchotenine contains the original hydroxyl group of the alkaloid since it is readily acylated, and in addition is a carboxylic acid, the carboxyl group probably arising from the oxidation of the vinyl group $-CH:CH_2$ in cinchonine.

By the distillation of cinchonine with caustic alkalis, various quinoline and pyridine derivatives are produced.

The fact that cinchonine is a quinoline derivative is shown by the production of cinchoninic acid (quinoline $-\gamma-$ carboxylic acid) $C_9H_6N.COOH$, in quantity, when the alkaloid is oxidized with chromic acid. Further oxidation products, called respectively meroquinenine, $C_9H_{15}O_2N$, and cincholeuponic acid, $C_8H_{13}O_4N$, are also obtained, whilst quite recently Rabe has shown that by a slight modification of the conditions another derivative, which

he designates as cinchoninone, $C_{19}H_{20}ON_2$, may be isolated. Thus cinchonine may be considered as a quinoline derivative with a side chain in the γ-position, this chain of necessity containing the hydroxyl group of the alkaloid, otherwise a hydroxycinchoninic acid would appear on oxidation.

Cinchonine   Cinchoninic acid
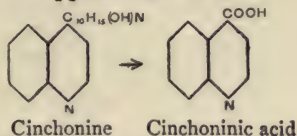
The constitution of cincholeuponic acid has been determined by Skraup from a study of its decomposition products, and has received confirmation at the hands of Wohl and Losanitsch, who have synthesized the acid. Cincholeuponic acid is a saturated dibasic acid, and contains the group $>NH$. The carboxyl groups are in the ortho-position, since the acid gives a fluorescein reaction when heated with zinc chloride and resorcinol. Again, the hydrochloride of the acid when heated with dilute sulphuric acid, to a high temperature, yields γ-picoline, and as the methiodide of methylcincholeuponic ester on treatment with caustic alkali is converted into a cyclopentane derivative which readily decomposes into dimethylamine and a tribasic acid when fused with potassium hydroxide, Skraup concluded that the acid was to be represented as
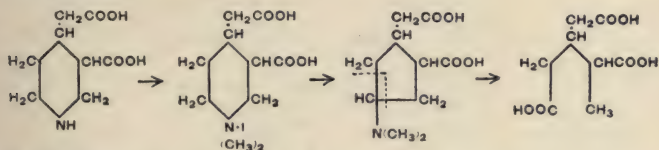
Cincholeuponic acid

Wohl and Losanitsch synthesized the acid from iminodipropionacetal, which on treatment with hydrochloric acid passes into $\Delta.3$-β-tetrahydropyridine aldehyde (I), the hydrochloride of the aldoxime of this latter compound on treatment with thionyl chloride yielding the hydrochloride of 4-chloropiperidine-3-nitrile (II). By elimination of hydrochloric acid from (II), Δ_3-tetrahydropyridine nitrile (III) is produced, and on condensation with

sodio-malonic ester yields an addition product, which on hydrolysis gave, among other products, two stereo-isomeric 4-pipecoline-3-ω-dicarboxylic acids (IV), these representing the two possible racemic cincholeuponic acids.
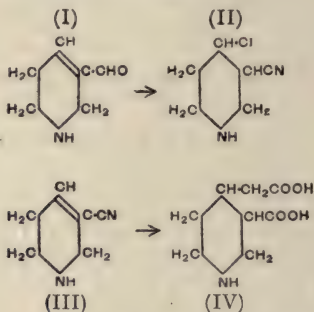
Meroquinenine, $C_9H_{13}O_2N$, is a secondary base which also contains a carboxyl group. On oxidation with sulphuric and chromic acids it yields cincholeuponic and formic acids, whilst a modified reduction with hydriodic acid in the presence of zinc dust yields cincholeupone, $C_9H_{17}O_2N$. Energetic reduction by hydriodic acid and phosphorus produces β-ethyl-γ-methyl pyridine, which is also formed when meroquinenine is heated with hydrochloric acid and mercuric chloride at 250° C. These results lead to the formulation of meroquinenine and cincholeupone as

Meroquinenine   Cincholeupone
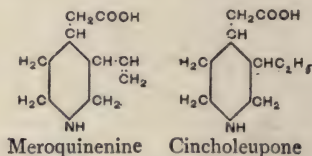
The results thus far obtained show that cinchonine contains a quinoline and a piperidine residue, which are of necessity united by a chain of carbon atoms attached to the γ-carbon atoms in each nucleus, this chain, on oxidation, giving rise to the carboxyl groups in meroquinenine and cinchoninic acid. This chain must also contain the hydroxyl group of the alkaloid since this group does not appear in either oxidation product. Further light is

thrown on the constitution of the cinchona alkaloids by the examination of the "toxins," a series of isomeric bases formed when the alkaloids are heated with dilute acetic acid for twenty-four hours. These bases contain the :CO and :NH groups, and differ from the alkaloids by their greater toxic properties, hence their name. Brunner showed that these toxins yield a monoisonitroso derivative, and hence do not contain the group $-CH_2.CO.CH_2-$ as was at one time thought probable.

Cinchonine $\longrightarrow$ Cinchotoxine.
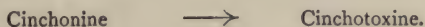
Cinchotoxine is a strong base, in which one nitrogen atom is tertiary and the other secondary in character. It is also a ketonic substance yielding an oxime and a hydrazone, absence of the aldehydic grouping being shown by the fact that methyl-cinchotoxine is not oxidized to an acid by silver oxide, and that dehydration of the oxime does not yield a nitrile.

In the conversion of cinchonine into cinchotoxine, that is of a tertiary base with a hydroxyl group into a secondary base with a keto-group, the groupings must undergo molecular rearrangement as follows :—

$$
\begin{array}{ccc}
:C.N: & & :CH \\
| & \to & | \quad + \quad HN: \\
-CH(OH) & & CO
\end{array}
$$

Koenigs considered that the :CO group in cinchotoxine was placed between two methylene groups, whilst Rabe, from the fact that it yields only a monoisonitroso-derivative, was of the opinion that the group is adjacent to the quinoline nucleus. A decision was arrived at by submitting the oxime of N-methyl cinchotoxine to the Beckmann reaction (using phosphorus pentachloride), the products obtained being cinchoninic acid (6%) and γ-amino-quinoline (43%), corresponding to the quinoline nucleus, together with N-methyl-β-vinyl-γ-aminoethylpiperidine and N-methyl homo-meroquinenine, from the piperidine nucleus.

13

$$C_9H_6N.COOH \quad \longleftarrow$$
$$\gamma\text{-}C_9H_5(NH_2)N \quad \longleftarrow \quad]\!\!- C_9H_6N.CO.CH_2.CH_2.C_7H_{12}N$$

$$CH_2.CH_2$$
$$CH_3N \quad CH.CH_2.CH_2.NH_2$$
$$CH_2.CH.CH{:}CH_2$$

$$CH_2.CH_2$$
$$CH_3N \quad CH.CH_2.CH_2.COOH$$
$$CH_2.CH.CH{:}CH_2$$
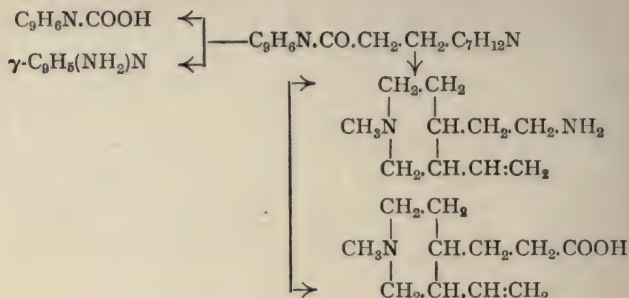
These results show that the :CO group in the toxines, and hence the .OH group in the alkaloid is linked to that carbon, which is directly attached to the quinoline nucleus. A similar result follows when the Beckmann transformation is applied to monoisonitrosocinchotoxine, the products obtained being cinchoninic acid and meroquinenine nitrile.

$$C_9H_6N.CO.C({:}NOH).CH_2.C_7H_{12}N \rightarrow C_9H_6N.COOH + HN \quad \begin{array}{c} CH_2.\,CH_2 \\ CH.CH_2.CN \\ CH_2.CH.CH{:}CH_2 \end{array}$$
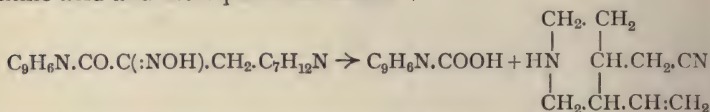
Thus cinchotoxine is to be formulated as—

$$CH_2 - CH - CH.CH{:}CH_2$$
$$CH_2$$
$$CH_2 \quad CH_2$$
$$C_9H_6N.CO \quad NH - CH_2$$
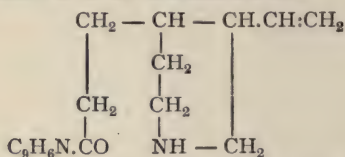
Rohde and Antonaz have arrived at a similar result from a study of the action of amyl nitrite and sodium ethoxide on the sodium salt of cinchotoxine. In this reaction the nitrite behaves as an oxidizing agent, and cinchoninic acid is formed in rather small quantity. The acid may, however, be obtained in quantitative yield by the action of nitrobenzene on the sodium salt in absolute alcohol. The products from the other portion of the molecule could not, however, be isolated, but it was shown that no meroquinenine was present, a fact which is accounted for by the assumption that the grouping $- CH_2.CO.CH_2 -$ is absent, the :CO group being directly linked to the quinoline nucleus.

The intermediate oxidation product cinchoninone, $C_{19}H_{20}ON_2$, obtained by Rabe in 1907, has the properties of a base, a phenol, and a ketone, whilst it also exhibits keto-enolic tautomerism. The production of a ketone, here seems to point definitely to the alkaloid cinchonine containing a secondary alcohol grouping $> CHOH$. Cinchoninone forms an oxime, and gives a benzoyl derivative, but since both nitrogen atoms are tertiary in character, it follows that the acyl group must be linked to an oxygen atom. On treatment with nitrous acid, cinchoninone yields cinchoninic acid and an oxime, $C_9NH_{13}:NOH$,

$$C_{19}H_{20}ON_2 + ONOH \rightarrow C_9H_6N.COOH + C_9H_{13}N:N.OH.$$
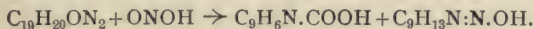
a reaction analogous to the preparation of diacetyl monoxime from ethyl methylacetoacetate, and hence pointing to the existence of the grouping $.CO.CH <$. The oxime still contains the tertiary nitrogen atom of the other portion of the molecule, and on hydrolysis yields meroquinenine and hydroxylamine. Hence, knowing the constitution of meroquinenine (I), that of the oxime must be (II), which leads to cinchoninone being (III) and cinchonine (IV).
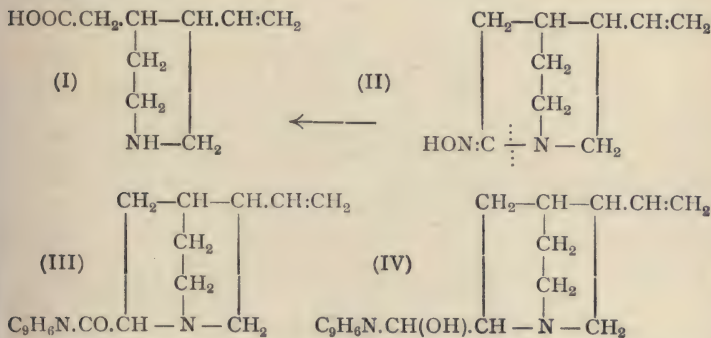
In precisely the same manner quinine yields a ketonic derivative quininone, $C_{20}H_{22}O_2N_2$, and this on treatment with nitrous acid is decomposed into quininic acid and meroquinenine. Consequently, as quininic acid is known to be *p*-methoxyquinoline-*γ*-carboxylic acid, quinine must be
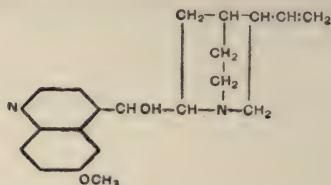
The formula given above for cinchonine is also rendered probable by analogy with narcotine, for just as cinchonine may be converted into cinchotoxine, so Rabe has shown that narcotine when heated with dilute acetic acid passes first, probably, into its isomer, gnoscopine, and then decomposes into cotarnine and meconine, together with a keto-base nornarceine—
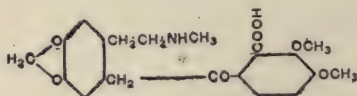
from which it would appear probable that narcotine and cinchonine contain the group $> N.CH.CH(OH) -$ in common.

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CHAPTER V

THE RELATION BETWEEN THE COLOUR AND CONSTITUTION OF CHEMICAL COMPOUNDS

THE gradual development of synthetic chemistry in recent years, and the increasing knowledge of the relative structure of chemical compounds, has led to a desire to express a relation between the structure of compounds and their physical properties. In this way many important generalizations have been made, and, knowing the constitutional formula of a compound, one is able to deduce in many cases a number of its physical constants with a fair degree of accuracy. Since the colour of a substance is one of its most striking properties, many attempts have been made by different investigators to deduce a connection between the colour and structure of compounds.

At first, it was only "colour" of wave length between the limits of the visible spectrum that was taken into consideration, but recently much investigation has taken place in the (to the eye) invisible "ultra-violet" region of the spectrum, and it is from these ultra-violet spectra that much information is to be obtained in the elaboration of the present-day dynamic theories of colour.

The first attempt to correlate colour with structure was due to Otto Witt, and was known as the auxochrome-chromophore theory, and it may be noted in passing that it still gives, in a limited number of cases, the best explanation of the known facts (Kauffmann, *Ber.* 1906, **39**, 1959). In the development of this theory it was noticed that the introduction of certain groups into carbon compounds tended to cause a colourless compound to become coloured, and as a result of this property Witt designated these groups as " chromophores." The introduction of a single chromophoric group, however, has not usually a sufficiently

marked effect in the production of colour of visible wave length ; but if certain other groups are introduced in addition into the chromophoric nucleus (or chromogen), the auxiliary effect is almost always sufficient to produce visible colour. This second group of radicals is known as the auxochrome group, but it must be borne in mind that auxochromes alone do not produce colour when they are introduced into a colourless molecule. Thus, on this theory a coloured compound is to be regarded as consisting of a neutral radical to which are attached one or more chromophores, and one or more auxochromes.

The principal chromophoric groups are the *carbonyl* $> C{:}O$, *thionyl* $> C{:}S$, *nitrile* $- C{\vdots}N$, *azo* $- N{:}N -$, *azoxy* $- N{:}N -$, *nitroso*
$$\overset{\cdot}{\underset{\cdot}{-O-}}$$

$- N{:}O$, and *nitro* $- N\overset{/\!/O}{\underset{\backslash\!\backslash O}{}}$ groups, and of these the carbonyl, azo and nitro-groups are the most important. The carbonyl group by itself does not produce visible colour, but two carbonyl groups in juxtaposition usually produce coloured substances. When the two groups are more remote from each other, colourless substances again result, striking examples of such results being seen in the case of the simple α, β and γ diketones.
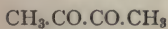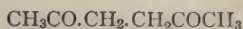
$CH_3.CO.CO.CH_3$	$CH_3.CO.CH_2.CO.CH_3$	$CH_3CO.CH_2.CH_2COCH_3$
Diacetyl	Acetyl-acetone	Acetonyl-acetone
Yellow	Colourless	

In the aromatic series, the presence of one carbonyl group often appears to have a disproportionately large effect, but this may perhaps be explained by the conception of the double bonds in the molecule as possessing an auxochromic character. Thus fluorenone is highly coloured, and that the colour does in this case depend on the presence of the carbonyl group is shown by the fact that if the ketonic oxygen be replaced by chlorine, the resulting di-chloro derivative is colourless.
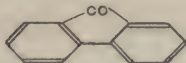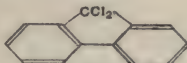
Coloured   Colourless

In both the aromatic and aliphatic series it is invariably found that compounds containing the azo-grouping are highly coloured, even the simplest members of the series, namely diazomethane and diazoethane, being yellow. It is, however, in the benzene series that the effect is most marked, azobenzene, for example, crystallizing in the form of large scarlet plates. The azo-group is regarded as one of the strongest chromophores, though when found as a constituent group of a closed ring system, its effect is not nearly so marked, as, for example, in tolazone, which is only slightly coloured.
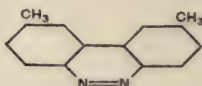
The nitro-group is also a most important chromophore, not so much by reason of the magnitude of its effect, but rather by reason of the ease with which it may be introduced, and the generality of its action.

The chief auxochromes, arranged in order of magnitude of effect by Kauffmann, mainly on the evidence of magnetic rotation constants, are the *acetoxy* ($-OCOCH_3$), *methoxy* ($-OCH_3$), *acetamino* ($-NHCOCH_3$), *amino* ($-NH_2$), and *dimethyl* and *diethyl* amino groups. In addition to these there is also the hydroxyl group, the auxochromic effect of which varies considerably with its orientation in the molecule. As has been mentioned, Witt's theory assumes the action of the auxochrome to lie in intensifying the effect of the chromophore. This action is explained to be due to a finer display of forces within the molecule, caused by the strain consequent on the introduction of the auxochrome. Thus, as Kauffmann says, "The benzene ring is no dead unalterable structure, but a most delicate picture, which on the slightest touch at once alters its properties, to a greater or less extent, in reply."

Among the auxochromic groups it is found that the amino-group and its derivatives exert a greater effect than the hydroxyl group and its corresponding derivatives, for example, whilst paranitro-aniline is coloured bright yellow, paranitro-phenol is

quite colourless.   Again, alkylation of the amino-group tends to produce more colour, whilst the alkylation of the hydroxyl group has apparently no settled effect, thus Liebermann has shown that the alkylation of alizarine and isoanthraflavic acid causes the absorption bands to move toward the violet end of the spectrum, whilst similar treatment of anthraflavic acid and quinalizarin moves the bands towards the red end.   The introduction of several auxochrome groups has a cumulative effect, but in the case of single groups the maximum effect appears when the auxochromic group is in the ortho- or para-position to the chromophore.   This is well illustrated in the case of the fuchsine dyestuffs, the effect of the position of the auxochromic group

(NH$_2$) in relation to the chromophore $\left(= \left\langle \underset{}{\overline{\underline{}}} \right\rangle = \right)$

being shown in the colur transition from violet to blue-green and green, in the annexed examples.

Violet   Blue-green   Green
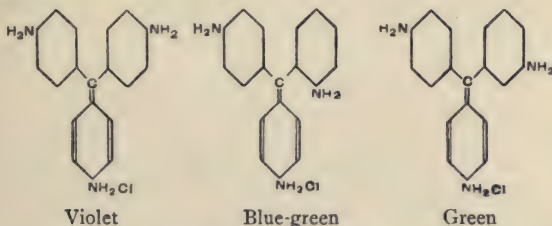
The auxochrome-chromophore theory as thus outlined has undoubtedly been of great use in the development of the theory of colour, since it has satisfactorily generalized what might have been merely a disjointed collection of facts, but in many cases it is unsatisfactory, in that it occasionally leads to anomalies.   This is seen, perhaps, best in the azo-series, where addition of the auxochromes $-NH_2$ and $-OH$ has no effect in the direction indicated by theory, or indeed in some cases has a precisely opposite action.

The next development in theory was due to Armstrong in 1888, and was known as the "quinonoid" theory of colour.   All quinones appear to be highly coloured compounds, and Arm-

strong pointed out that most coloured compounds could be formulated as quinone derivatives, and this quinonoid structure was regarded by him as the cause of colour. The simplest quinone (benzoquinone) is of a deep golden yellow colour, and that the colour effect is due to the special grouping in the molecule, and not merely to mutual reinforcement by the carbonyl groups is clearly shown by the fact that cyclohexane-dione-1-4 is colourless, while the colour effect still persists in other quinonoid compounds. In considering examples based on this theory it is not necessary that the quinone oxygen atoms should be present, any other group united to the carbon atoms in the position 1.4, provided that it is a bi-valent group (the double bonds being essential), will suffice, thus, for example, in quinone diphenyl-diimide,

$$C_6H_5N = C_6H_4 = NC_6H_5,$$
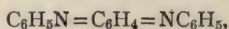
which is brown red in colour, the group $C_6H_5N =$, satisfies the necessary conditions, whilst in the "aurine" group of dyestuffs a simple quinone grouping is present.
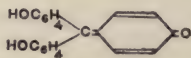
Again, a series of coloured hydrocarbous such as, for example, tetraphenyl-p-xylylene,

also afford a striking example of the effect of a quinonoid grouping in producing colour.

The almost universal presence of a quinonoid structure in coloured compounds gave great support to this theory, which was, however, subject to much hostile criticism, and it seems necessary to point out that although all quinones may be coloured it does not *necessarily* follow that all coloured substances should be quinonoid in structure. In view of this obvious fact it cannot be too strongly urged that when a coloured substance admits of a quinonoid formulation, all the evidence,

both chemical and physical, should be thoroughly considered, and the case treated on its merits.

Among cases which have given rise to considerable discussion as to the validity of the quinonoid theory of colour, that of phenol-phthalein and its alkali salts has caused, perhaps, the most interest.   This substance is in neutral or acid solution, quite colourless, but in the presence of caustic alkali exhibits a deep red colour.   According to Ostwald, the phenomenon is to be ascribed to simple ionization.   He regards phenol-phthalein as unionized, but yielding in alkaline solution a coloured ion.   On the quinonoid theory the change is attributed to a change of configuration from the benzenoid to the quinonoid type of structure, it being assumed that the lactone ring in the molecule is broken, and the salt of a quinonoid carboxylic acid is produced.
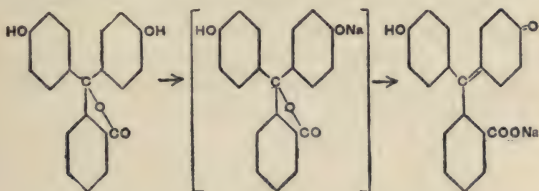
Somewhat later it was found that the addition of excess of alkali or alcohol to the solution, tended to destroy the colour initially produced.   According to the ionization theory one has to suppose that excess of these reagents would tend to repress any electrolytic dissociation in the solution, and so the number of coloured ions in the solution would gradually diminish, and the colour of the solution become gradually fainter and fainter as ionization diminished.   The quinonoid theory found considerable support in the work of Nietzki, who showed that by working under suitable conditions, two isomeric ethers could be obtained from the potassium salt of fluorescein, one being colourless and unaffected by the addition of aqueous alkali, the other, coloured, losing one . ethoxy-group under the influence of alkali.   This result necessitates that the non-coloured and coloured compounds should be represented as

Colourless   Coloured
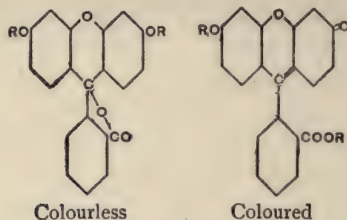
Further evidence favouring the quinonoid formulation of the coloured alkali salts of phenol-phthalein is given by the work of Perkin and Green. These authors suggest that the colour changes produced by the addition of an excess of alkali may be due to the destruction of the quinonoid grouping by the addition of a further molecule of alkali, and consequent production of a colourless carbinol compound, which on heating becomes dehydrated, and reverts to the red quinonoid form.

Colourless.   Red.   Colourless.
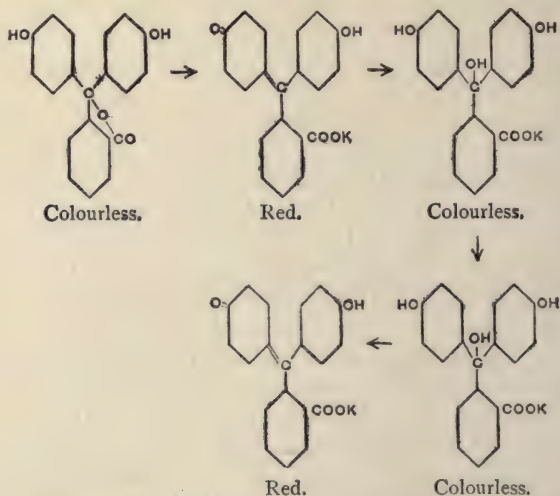
Red.   Colourless.

A conclusive proof of the quinonoid character of this type of compound was given by Meyer and Marx in 1907, when they succeeded in preparing a coloured ether of a brominated phenol-

phthalein, which very easily isomerized into a colourless
ether.[1]

Colourless.   Coloured.
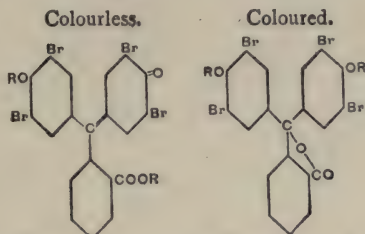
The change from the colourless phenolphthalein to its red
alkali salt is thus apparently to be regarded as accompanied by
a radical change in structure of the two substances.   This view
does not necessarily militate against any idea of ionization, for
undoubtedly the phenolphthalein salts do contain a red ion, the
chief point to be borne in mind is that the process of salt forma-
tion is accompanied by a change of constitution.   It is possible
that the ionic and chemical theories are here complementary,
since for a substance to act as an indicator it must be a weak
acid or a weak base, but the ion which it forms must possess
a different structure from the parent substance, the latter body
thus being a ψ-acid or a ψ-base. Phenolphthalein may be regarded
then, as showing the following equilibrium in solution :—

$$O:X_u.H \rightleftarrows X_v.O.H \rightleftarrows X_vO' + H^{\cdot}$$
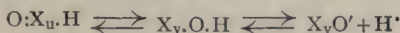
X_u and X_v representing respectively :—
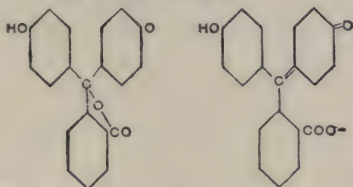
X_u is the more stable configuration, and the acid is very weak
(the dissociation constant of phenolphthalein as measured by

[1] Somewhat later in the same year they obtained similar ethers of the non-
brominated phenolphthalein.

Salm being 8.0×10^{-10}). Therefore $X_v.O.H$ and its ions are only present to a very small extent in neutral solution, and the absorption due to X_u is observed (this absorption is in the ultraviolet region of the spectrum, and the substance thus appears colourless). The addition of bases (*i.e.* hydroxyl ions) removes the hydrogen ions, and the colour due to the X_v configuration then makes its appearance.

The quinonoid structure of the phenolphthalein salts has also been adversely criticized by Silberrad, who has prepared compounds of similar type, which he claims cannot possibly undergo change to a quinonoid structure. But, as has been pointed out by Green, this difficulty is removed if the presence of quadrivalent oxygen in the molecule be assumed (see p. 231).

Much discussion has also taken place with regard to the constitution and colour of the azo-compounds, reference to which will be made later. No review of the quinonoid theory can be considered as complete without reference to its extension to the case of the nitro-compounds, more especially to the nitro-phenols, for it is in connection with these compounds that Hantzsch's generalization that "a fundamental change of colour on salt formation is due to a change in the structure of the compound," was substantiated. The nitrophenols are in general, weakly coloured substances, their alkyl derivatives being usually colourless. On the other hand, their alkali salts are, as a rule, highly coloured, and it was first suggested by Armstrong that this change of colour was due to an intramolecular change, salt formation being accompanied by the production of a quinonoid structure.
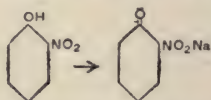
The experimental confirmation of this hypothesis was chiefly due to Hantzsch, who in a series of papers developing a theory of ψ-acids had pointed out that a marked change in properties of a substance on salt formation always connoted a structural change. This idea, of course, gave to Armstrong's conjecture an air of probability, and in 1906 really direct confirmation was afforded

by the isolation of two isomeric ethers of *o*-nitrophenol, one coloured and the other colourless. The coloured ether is labile, and passes readily into the colourless stable form, which is identical with *o*-nitroanisole. The two forms may, therefore, be represented by the general formulæ—

$CH_3O.C_6H_4.NO_2$ $O:C_6H_4:NOOCH_3$
True nitrophenol ether   *aci*-Nitrophenol ether
Colourless ; stable   Coloured ; labile

This structure of the *aci*-compounds receives corroboration from a consideration of certain coloured mercury compounds which do undoubtedly possess such an orthoquinonoid configuration. Thus the mercury salt of *o*-nitrophenol when heated, undergoes internal condensation with the production of a compound, which, by analogy, with compounds prepared by Dimroth, and by comparison with similar compounds obtained from trinitrophenol, can only be represented as—
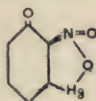
This compound is thus similar to the ether, and is coloured. The free nitrophenols, which are coloured, are assumed to consist of a solid solution or equilibrium mixture of the two dynamic isomerides, the colour intensity depending upon the proportion of the *aci*-constituent present. Every case of colour in the nitrophenol group is explained in the light of these facts. In the case of picric acid it may be noted that the *aci*-ethers are red in colour, whilst the alkali salts are much lighter in colour, and this is explained by the existence of two series of *aci*-ethers, a light and a dark coloured one, the metallic picrates corresponding to the light coloured series.

The change of colour in the nitrophenols is not only brought about by conversion into their salts, but also by rise of temperature, and by solvents, thus, whereas light petroleum gives a colourless solution, water, with its greater ionizing power, produces a certain amount of the *aci*-form. Hantzsch does not admit that

14

ionization alone produces colour, but considers the change is entirely structural in the first instance, and ionization is only a secondary phenomenon, and draws the conclusion that the idea of chromophore and auxochrome as separate factors in colour production does not hold, but that the phenomenon of colour is the effect of a chemical interchange which is promoted by their association in the same compound.

$$HO.C_6H_4.NO_2 \quad \rightarrow \quad O:C_6H_4:NO_2H$$

This hypothesis of Hantzsch has been criticized adversely by Kauffmann, who defends the auxochrome theory on the grounds of the change in position of the absorption band produced in benzene by the introduction of substituent groups, and on the existence of coloured ethers, such as nitroquinol dimethyl ether, the existence of Hantzsch's colourless ether being ascribed to the weak auxochromic character of the methoxy group. Hantzsch defends his position by pointing out that the absorption spectra cannot determine the presence or absence of auxochromic groups, because no relation has been shown to exist between them, and he also doubts the purity of the yellow form of nitroquinol dimethyl ether. Hantzsch considers that all nitro-compounds are colourless, and that the true nitroquinol dimethyl ether is thus colourless and exists as such in solutions in non-dissociating or feebly dissociating solvents, basing his claim on the fact that the molecular refraction of the ether in feebly dissociating solvents is only slightly greater than the calculated value, whilst in solutions in strongly dissociating solvents a pronounced exaltation of the value is observed. In a later paper Kauffmann, however, points out that Hantzsch contradicts himself, since he has already pointed out that nitrobenzene shows absorption in the extreme violet, which is only another way of saying that it is not colourless; and also that it is known that substances containing auxochromes in the benzene nucleus exhibit abnormally high molecular refraction, consequently the true nitroquinol ether must be that form existent in solutions in highly dissociating solvents, that is the yellow modification.

Reference may be made here to an idea mooted in 1905 by

Baeyer, who found that the sulphates of *p*-trichloro-, and *p*-tri-iodo-triphenyl carbinols are highly coloured salts which show no tendency to lose halogen on treatment with silver nitrate, a result hardly compatible with the view that these compounds possess a quinonoid structure,

for the chlorine atom in the quinone nucleus of such a compound should be easily detachable.   Acting on Gomberg's idea that the yellow solutions of triphenylmethyl chloride in certain solvents are due to ionization, Baeyer introduces a distinction between an ionizable and a non-ionizable valency, the ionizable bond being represented as ∼∼∼∼.   In the triphenylmethane series this is called the carbonium bond and is responsible for the colour. On this principle the sodium salt of phenolphthalein is represented as (I), aurin as (II), and the azo-series as (III).
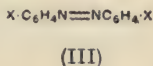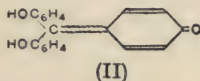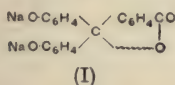
Owing to its vague and somewhat indefinite powers, this idea of the carbonium valency has not received much support.

Thus far a somewhat restricted view of colour has been taken, as, for example, in the work of Hantzsch, whose explanation of colour phenomena is a statical one, depending upon a particular structure, and it would seem advisable that the previous conceptions should be extended.   Colour is produced by selective absorption of part of the spectrum and, in addition to the ordinary spectrum, the rays of which affect the eye and so produce visible colour ; there are other rays of exactly the same nature which differ from ordinary light rays only in rapidity of vibration.   The human eye is unable to detect and appreciate waves longer than those of red light or shorter than those of violet light.   The rays of the invisible spectrum though without effect on the eye may be detected by the photographic plate, and it has been shown by Hartley and others that many substances which are

designated as colourless show selective absorption in the invisible (to the eye) ultra-violet region of the spectrum. There is no essential physical difference between selective absorption in the ultra-violet and in the visible spectrum, the distinction commonly drawn between "coloured" and "colourless" substances being in most cases a subjective one, depending on the limited capabilities of the human eye, and consequently any thoroughly scientific treatment of the subject of colour must recognize the existence of these theoretically "coloured" substances. Since absorption of light means absorption of energy the question may be asked, "To what use is this energy put?" and it seems most reasonable to consider that it is used up either in causing or reinforcing certain vibrations in the molecule, the frequencies of these vibrations being equal to those of the particular wave-lengths of the light absorbed. The view appears still more reasonable when the numerous cases in which light either induces or modifies reactions is taken into account.

By increasing the molecular weight of a compound one may suppose that the vibrations of the molecule, associated with the absorption of light, would become slower, and in this way the absorption might be shifted from the ultra-violet region into the visible spectrum. By such means a colourless body might become coloured; but there is no need to suppose a constitutional change has taken place to explain the production of colour, since it may be merely the result of adding to the weight of the vibrating structure, thereby rendering it less active. By taking into consideration such ideas as these a dynamical foundation for the relation of colour to structure has been introduced, one of the earliest attempts at such being given in 1900 by Hewitt to explain the phenomenon of fluorescence. Fluorescence is the absorption of radiant energy of definite wavelength, and the emission of the same energy after it has been reduced in vibration frequency, and, in the opinion of Hewitt, one would consequently expect to find that it is thus a property of substances which are capable of existing in tautomeric forms. If one of the forms is symmetrical in structure, then in order to pass into the other configuration, either of two displacements is

necessary, these being equal in magnitude but opposite in sign ; for instance, with fluorescein itself the phases may be represented.
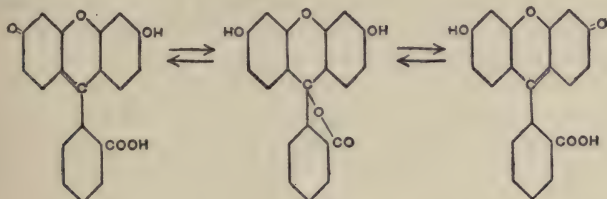
and a molecule which shows a tautomerism of this type might undergo continual and frequent change. The energy absorbed when the molecule possesses one configuration will consequently be emitted to an appreciable extent when it passes into the other configuration. Since it may be considered as certain that the vibration frequencies are different in the two forms (for the absorption spectra of the diethyl ethers of the quinonoid and lactone structure are quite different), every opportunity is given for the transformation and degradation of the energy which is necessary to explain the fluorescence.

The next attempt to show that intramolecular activity is the true explanation of colour came in 1905 from Baly and his co-workers, who have made a study of the absorption spectra of a large number of compounds. In carrying out these observations the usual method of procedure is to determine the variation of absorption with concentration, of solutions of substances, and to express these results in the form of a curve, a characteristic and quantitative record of the absorption or colour thus being obtained. By using this method it is found that substances of similar structure give the same type of curve, and this fact has been used with some degree of success to settle doubtful cases of constitution, although it may be urged in objection to the method that preconceived notions as to constitution may lead a too hasty observer to imagine and to exaggerate similarities in curves. Taking all facts into consideration, one is led from the study of absorption curves to adopt a modified view of Hantzsch's original

"Umlagerungs" theory, and to say that a change in the absorption curve of a compound affords evidence of some internal change in the molecule. Baly has gone somewhat further than this, and has offered some suggestions as to the nature of the vibrations associated with selective absorption, and finally comes to the conclusion that the origin of colour exists in the vibration of the valencies.

From the reactivity of certain diketones to chemical reagents, and from certain peculiarities shown by their absorption spectra, Baly was led to the conclusion that the diketones could not be adequately represented by static formulæ, since their properties indicate a state of dynamic isomerism. It is found, for example, that the carbonyl group in aceto-acetic ester is far more reactive towards sodium bisulphite than would be expected from current ideas on steric hindrance, the reactivity being greater than either that of acetone or methyl ethyl ketone. Usually the presence of a heavy group adjacent to the active group either retards or inhibits the reaction, and consequently it might be expected that aceto-acetic ester would be the least reactive of the above-mentioned compounds. It is evident, then, that some new influence has appeared which tends to mask or modify the steric hindrance due to the more voluminous group. Acetone shows very little sign of tautomeric change, whilst, on the contrary, aceto-acetic ester exhibits a very marked keto-enolic tautomerism. Baly ascribes the reactivity of the carbonyl group in such compounds to the actual process of tautomeric change,

$$CH_3C(OH):CH.COOC_2H_5 \rightleftarrows CH_3.CO.CH_2.COOC_2H_5$$
$$\text{(I)} \qquad\qquad\qquad\qquad \text{(II)}$$
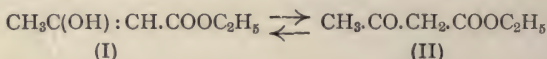
thus, when a molecule of configuration (I) passes into the form represented by (II), it may be assumed from analogy with the behaviour of atoms in the nascent state that this "nascent carbonyl group" is endowed with a much greater reactivity than that possessed by the ordinary non-nascent carbonyl group, which is present in such a compound as acetone.

This reactivity need not, however, be occasioned purely by the wandering of the hydrogen atom from oxygen to carbon;

it may be due to some finer display of forces within the molecule, which manifests itself in the production of the characteristic absorption band in the β-diketone spectrum. The condition into which the hydrogen atom is thrown as a result of this play of forces may be termed a condition of " potential tautomerism," and the hydrogen atom will consequently possess a reactivity somewhat similar to that of an hydrogen ion.

Ethyl pyruvate, $CH_3.CO.COOC_2H_5$, is another ketonic substance which is extremely reactive toward sodium bisulphite, and when its absorption spectrum is examined it is found to give a band much nearer the red end of the spectrum than the band shown by aceto-acetic ester. The origin of this band may be attributed to

(i) the keto-enolic transformation $CH_3.CO- \rightarrow CH_2{:}C(OH)-$
(ii) the interaction of the :CO group with the $COOC_2H_5$ group.

The first of these explanations is impossible, since if keto-enolic change were responsible for the absorption, the band should occupy approximately the same position in the spectrum as that of aceto-acetic ester and its derivatives. Again, the ethyl pyruvate molecule is lighter than that of ethyl aceto-acetate, and one would expect the band of pyruvic ester to be lower down in the ultra-violet spectrum than that of aceto-acetic ester, whereas the reverse is the case. As other α-diketones give similar results, Baly considered that the band in question was due to the action of the two carbonyl groups on each other, and that it was produced by the change

$$CH_3.C{-}C.OC_2H_5 \rightarrow CH_3.C{=}C.OC_2H_5$$
$$\overset{\|}{O}\ \overset{\|}{O} \quad \leftarrow \quad \overset{|}{O}{-}\overset{|}{O},$$
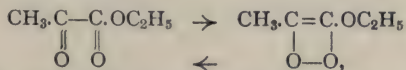
these formulæ representing different phases of the substance. This special type of oscillation was called "isorropesis" ($\iota\sigma\sigma\rho\rho\sigma\pi\iota\alpha$, an equipoise). The isorropesis band of the α-diketones is in the blue region of the spectrum, and consequently these compounds appear yellow.

In order to account for isorropesis (*i.e.* oscillations between the residual affinities of adjacent atoms) it is absolutely necessary to have some exciting or disturbing influence present, thus, for

example, in diacetyl CH_3CO $CO.CH_3$ this influence is furnished by the hydrogen atoms of the methyl groups. In this compound there is an attraction exerted on the hydrogen atoms by the oxygen atoms, with the result that the residual affinities on the two oxygen atoms tend to undergo alteration, evidence of this potential isomerism existing in the incipient formation of a keto-enol type of band in the absorption curve of diacetyl. Hence the residual affinities of the two oxygen atoms are being slightly disturbed, and it is owing to this disturbance that the new oscillation occurs.

The dioxime of diacetyl is colourless, yet apparently there exists a condition for isorropesis in the molecule, although no selective absorption is shown. This condition is, however, explained by Baly on the assumption that the residual affinity of the nitrogen atoms exerts no attraction on the hydrogen atoms of the methyl group, and consequently no disturbance is set up, therefore there is no isorropesis and no colour. Having in this way attempted to express the idea that intramolecular activity is the cause of colour, Baly proceeded to defend his position by an extended study of absorption spectra. He found that the peculiarities exhibited by the aliphatic diketones were reproduced in the quinones, and the two phases of benzoquinone were therefore represented as
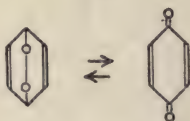
When once isorropesis had been detected in quinones, the extension of the theory to include all colour at once followed, for it simply became a new expression of the old quinonoid theory, the quinonoid structure being regarded as the statical representation of such an internal oscillation as affects the visible region of the spectrum. The colour of the nitroanilines and nitrophlenos is ascribed in the same way to oscillations set up by the change of the residual affinities of the nitrogen and oxygen, and the two nitrogen atoms respectively :—
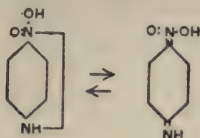
p-nitrophenol in alcoholic solution, and its sodium salt, are represented by—
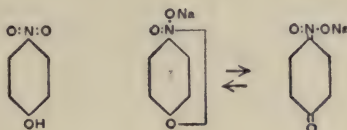
The free nitrophenol is statical and colourless, the sodium salt dynamical and coloured. In a recent paper Baly has abandoned his original view that the colour and absorption of the nitrophenols and nitroanilines is due to the existence of the quinonoid configuration, and considers that, in nitro-compounds generally, the absorption bands are due to isorropesis between the nitro-group and the residue of the molecule.

Very little greater generalization is apparently given by this theory than by the older theory, and it can scarcely be said that the newer phraseology gives any clearer explanation. It, however, claims consideration, since an attempt is made to recognize that not the mere orientation of the groups in the molecule, but an internal vibration among the groups, is the cause of colour.

In 1907 Hewitt and Mitchell, in a paper dealing with the azo-compounds, attempted to give to the quinonoid theory a dynamic interpretation. By a consideration of the ordinary formulæ it is made clear that compounds of a quinonoid type can be represented as containing a chain of atoms linked together alternately by single and double bonds. If now in such a substance, a system of vibration—

$$=C-C=C-C=C- \quad \underset{\longleftarrow}{\longrightarrow} \quad -C=C-C=C-C=$$

be assumed, it is obvious that the longer the chain of alternate single and double bonds, the longer will the vibration take to travel the

whole length of the system, hence the slower the molecular vibration. With slower molecular vibration it is clear that a greater proportion of red rays will be absorbed ; or, expressed otherwise, the compound will appear more blue in shade. The method or experiment adopted was to compare the absorption curve of the azophenol with that of its *p*-nitroderivative and the sodium salt of the nitro-compound, so that in this manner the effect of the introduction of the nitro-group could first be ascertained, and secondly a direct lengthening of the chain, without the introduction of a new substance, was obtained. Thus, with the azophenol and azo-α-naphthol compounds and their salts the configurations may be expressed—
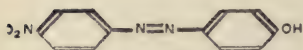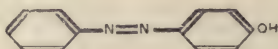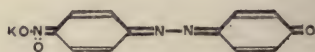
5 double, 4 single   6 double, 5 single
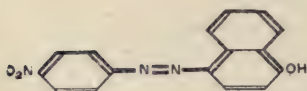
7 double, 6 single.   8 double, 7 single.
Alcoholic soln. RED.   Alcoholic soln. VIOLET BLUE.

As Hewitt and Mitchell observe, the chief oscillation frequency is less, the longer the chain of alternate double and single linkages which exist in the molecule, and in estimating the number present, one is only justified in following the structure round one side of the ring until a para-position is reached, for if carried further, the action becomes retrogressive, and consequently no part of the particular displacement under consideration, but a part of the succeeding or return displacement. Many compounds were examined from this standpoint, and it was found that in each case the theory fitted in with the experimental facts. No attempt has yet been made to give any connection between the length and nature of the chain and the wave-length of the

light absorbed, but it would certainly appear that on theoretical as well as on practical grounds the discovery of such a relationship is not improbable.

One may note that two series of compounds exist which cannot be brought into harmony with any of the colour theories yet proposed, namely, the fulgenic acids (and fulgides) and the fulvenes.

In the case of the fulgenic acids and fulgides, which are respectively of the type—

$$R_2.C : C.COOH \qquad\qquad R_2C : C.CO$$
$$\mid \qquad\qquad and \qquad\qquad \mid \qquad \mid$$
$$R_2C : C.COOH \qquad\qquad\qquad O$$
$$\mid$$
$$R_2.C:C.CO$$
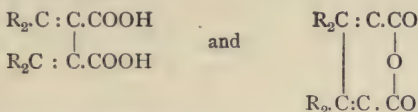
the auxochrome-chromophore theory leads perhaps to the fewest anomalies. The double bonds, carbonyl groups, and, when present, the phenyl groups are regarded as colour centres, the density of grouping of these being alleged to afford sufficient explanation of the colour produced. Adherents of the quinonoid theory have, however, suggested that the fulgides can be formulated as analogues of benzo-(o)-quinone—

$$R_2C : C.C : O \qquad\qquad OC = CO - CH$$
$$\mid \qquad\qquad\qquad \mid \qquad\qquad \parallel$$
$$O \qquad\qquad\qquad HC = CH - CH$$
$$\mid$$
$$R_2C : C.C : O$$
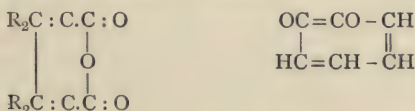
but one cannot consider that this is the case, for the essential quinonoid grouping must of necessity be absent from a five-membered ring system containing an oxygen atom as a constituent. The phenyl derivatives, which are the most highly coloured, contain a chain of alternate single and double bonds, and it is noteworthy that the longer this chain is, the deeper the colour becomes.
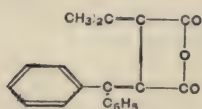
5 double, 4 single
Citron yellow
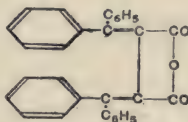
6 double, 5 single
Blood red

The chain, however, is not long enough of itself to explain the colour, for stilbene, which contains a chain of five double and four single linkages, is colourless.

It may be claimed that the colour is due to isorropesis, between the carbonyl groups, but this also appears insufficient, for if isorropesis alone is responsible for the colour, then other dibasic acids of similar type should be coloured.

The simplest member of the fulvene class is—

$$
\begin{array}{c}
CH = CH \\
\quad | \qquad | \\
\qquad C = CH_2 \\
\quad | \qquad | \\
CH = CH
\end{array}
$$
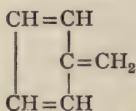
and here again no theory has been sufficient to explain the colour of these compounds. The chromophoric double bonds are too few in number, and the chain of alternate double and single linkings is too short. The most successful explanation, perhaps because the least definite, is that which makes the fulvenes distantly analogous to benzoquinone.

Despite the activity shown in the experimental investigation of this subject, it is obvious that as yet no real relationship between colour and constitution has been determined, but it does appear probable that the final theory of selective absorption will be one which takes full cognizance of colour (using the term in its broadest sense) as an essentially dynamic property, the molecule being regarded not as a rigid structure, but as one whose components are held together by restraining influences, and which are capable of rapid oscillations. Although in particular groups much valuable generalization has been made, there is still very much unsolved, and it seems that progress will be made by a systematic study of selective absorption coupled with *chemical* evidence of constitution. In this way it may become possible to recognize in a general manner the groupings associated with the production of the vibrations giving rise to certain types of absorption, and hence to predict colour.

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CHAPTER VI

SALT FORMATION, PSEUDO-ACIDS AND BASES

IN the study of organic compounds one finds that ammonia and allied compounds (*e.g.* phosphine, arsine, etc.) are capable of giving rise to salts, to which correspond the strong bases of the type

$$NR_4OH, \ PR_4OH, \ AsR_4OH$$
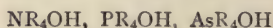
derived from the corresponding "X"-onium salts. A similar type is also found corresponding to the weak acid H_2S, which gives rise to the strong sulphonium bases $R_3S.OH$; the salts in this case being obtained by the action of alkyl iodides on the neutral alkyl sulphides.

$$R_2S \quad \overset{RI}{\rightarrow} \quad R_3SI \quad \rightarrow \quad R_3S.OH$$
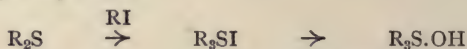
An examination of such compounds shows that in nearly all cases the grouping elements are of a positive type. An instructive example is seen in the case of iodine, which, in the form of phenyl iodide, can in chloroform solution combine with chlorine to produce phenyl iodide chloride, the latter substance passing into iodosobenzene on treatment with alkali. Iodosobenzene possesses the properties of a weak base, and to some extent acts as an oxidizing agent, and its basic nature goes to prove the basic character of iodine in such compounds. It is also found that the introduction of an iodoso-group into benzoic acid reduces the acidic strength very greatly, iodoso-benzoic acid being a much weaker acid than benzoic acid, and partaking more of a phenolic nature. These facts led V. Meyer in 1894 to attempt the isolation of derivatives of the iodonium base, $HI(OH)_2$, in which effort he was to a certain extent successful, the diphenyl iodonium hydroxide and various salts being prepared. In the first experiments, iodosobenzene was placed in well-cooled sulphuric acid,

and it was found that the solution became brown and lost the power of liberating iodine from potassium iodide (a property shown by iodosobenzene). The solution is found to contain the sulphate of the new base, from which the iodide can be precipitated by the addition of potassium iodide. Since the iodide on distillation decomposes into phenyl iodide and di-iodobenzene, it must correspond to the molecular formula $C_{12}H_9I_3$,

$$C_{12}H_9I_3 = C_6H_5I + C_6H_4I_2,$$
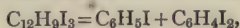
and the base and its sulphate must consequently be $C_{12}H_9I_2.OH$ and $(C_{12}H_9I_2)_2SO_4$, or

$$HO.I(C_6H_5).C_6H_4I \text{ and } SO_4.[I(C_6H_5).C_6H_4I]_2.$$
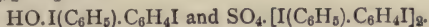
Numerous other salts have been obtained from the sulphate by double decomposition. The simple diphenyl iodonium hydroxide is obtained by triturating iodoso-benzene with moist silver oxide, the reaction depending on the fact that on exposure to sunlight the iodoso-compound is partly converted into iodoxy-benzene, $C_6H_5IO_2$, the two then reacting with the moist silver oxide as follows :—

$$C_6H_5IO + C_6H_5IO_2 + AgOH = AgIO_3 + (C_6H_5)_2I.OH.$$
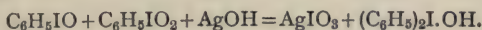
This hydroxide is a powerful base, but is only known in aqueous solution. It forms well-defined crystalline salts, and absorbs carbon dioxide with avidity. On the addition of sodium sulphide to the solution a yellow precipitate, resembling arsenic trisulphide, is produced, whilst if ammonium sulphide be used the precipitate resembles antimony sulphide.

The most recent element to be brought into the positive salt-forming groups is oxygen, the quadrivalency of which was suggested as long ago as 1864 by Naquet from the analogy existing between oxygen and sulphur, selenium and tellurium, all of which act as quadrivalent elements. It was not, however, until 1875 that Friedel isolated the hydrochloride of dimethyl ether, which was formulated by Wurtz as—

$$\overset{\text{H}}{\underset{|}{(CH_3)_2:O.Cl,}}$$
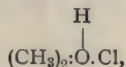
a conclusion accepted by Friedel, who was of opinion that the valency of the oxygen atom was dependent on the temperature in

this case. Van't Hoff indulged also in some speculations regarding oxygen, based on analogy to sulphur, and concluded that in oxygen and sulphur compounds, two bonds were prominent, whilst the third and fourth bonds, although weaker, are positive, and give to sulphur its basic nature, a similar condition existing with oxygen, thus rendering possible the combination of oxygen with the chlorides of less basic elements. At a somewhat later period (1876-1888) Baeyer and Fischer obtained addition products of fluorescein and sulphuric acid, whilst Dale and Schorlemmer similarly combined aurine with acids, and Wallach prepared such compounds from cineol and halide acids. The existence of these compounds was explained on the old valency theory, but it is obvious that a simpler explanation is possible if based on the higher valency of oxygen as was advocated by Heyes in 1888, to distinguish between such oxides as sulphur dioxide, carbon dioxide, etc., on the one hand, and barium peroxide, manganese dioxide, etc., on the other. Heyes considered the possibility of the existence of quadrivalent oxygen, and formulated his oxides as—

$$O=C=O \quad \text{and} \quad Mn=O=O.$$
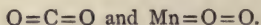
This idea was then applied by Meldola to the case of benzene-azo-β-naphthol, the acetyl derivative of which can be formulated as—

$$C_6H_5.N:N.C_{10}H_6OAc \quad \text{or} \quad C_6H_5N(Ac).N=C_{10}H_6=O,$$
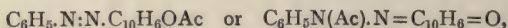
and in order to decide the question of structure Meldola isolated the reduction products of the acetyl compound, and obtained aniline, β-acetoxy-α-aminonaphthol, acetanilide, and α-amino-β-naphthol, from which he suggested that the acetylated azo-compound might be formulated as—
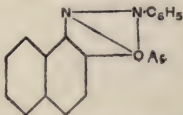
thus necessitating the presence of quadrivalent oxygen. This view, however, is not generally accepted, since Auwers, in 1904, showed that in hydrazones the acetyl group can wander from an

oxygen atom to a nitrogen atom, a process which will readily explain the formation of four different substances by the reduction of Meldola's acetyl derivative. Again, the anomalous behaviour of ethylene oxide in precipitating metals as hydroxides from solutions of their salts suggests the quadrivalency of the oxygen atom, the oxide in aqueous solution being represented as
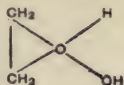
for in no other way does the production of metallic oxides seem possible.

This idea, however, of quadrivalency for oxygen was not generally accepted until the work of Collie and Tickle (1899) on dimethyl-pyrone was published. It had been shown at an earlier period that dehydracetic acid, when heated under pressure with fuming hydrochloric acid, yielded a compound, $C_7H_{11}O_3Cl$, which was shown by Feist to lose water, when dried over sulphuric acid, and to pass into $C_7H_9O_2Cl$. From this behaviour Feist concluded that it should be represented as a derivative of diacetyl-acetone.

$$CH_3.C(Cl):CH.CO.CH_2.CO.CH_3$$
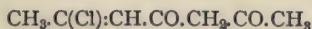
Collie and Tickle, however, pointed out that such a formula does not agree with the reactions of the compound, since it gives no colour reaction on the addition of ferric chloride, whereas diacetyl acetone gives a colour reaction. Again when dissolved in water it behaves as a mixture of dimethyl pyrone and hydrochloric acid, a reaction which seems very unlikely if the structure of the compound is, as advocated by Feist, with a chlorine atom directly united to carbon. The same substance can be prepared by the direct union of dimethyl pyrone and hydrochloric acid, and in aqueous solution possesses a strongly acid reaction, while from such a solution the dimethyl pyrone may be extracted by means of chloroform, and the amount of hydrochloric acid directly determined by titration. The compound in question may be recrystallized from water, and is relatively stable whilst in its reactions it behaves exactly as the salt formed from a strong

15

acid and a weak base. A similar series of salts were also obtained from other acids, such as hydriodic acid, nitric acid, hydrobromic acid, chlorplatinic acid, picric acid, etc., but the sulphate and acetate have not been obtained.

The ordinary graphic formulæ based on the simpler valency relations obviously fail to account for the existence of such salts, since, for example, the above hydrochloride would have to be represented as—

or $CH_3.C(Cl){:}CH.CO.CH_2.COCH_3$
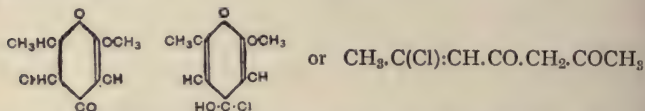
which will not allow for the production of dimethyl pyrone and hydrochloric acid when the hydrochloride is decomposed by water. But regarding these compounds as salts of weak bases and strong acids, and bearing in mind their resemblance to the corresponding $\alpha\alpha$-dimethyl-γ-lutidone compounds, a solution of the difficulty is obtained by the consideration of the oxygen atom as quadrivalent, thus—
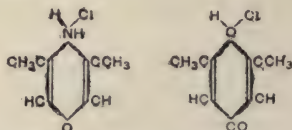
and, moreover, if oxygen can replace P, N, and S in bases, then these oxygen compounds can be regarded as derivatives of the hypothetical *oxonium hydroxide* $OH_3.OH$, just as the similar compounds of nitrogen, phosphorus, sulphur, and iodine are regarded as derived from the hypothetical bases NH_4OH, PH_4OH, H_3SOH, and $H_2I.OH$, and these salts can consequently be designated as *oxonium*[1] salts. The solutions of such salts have the characteristic properties that are to be expected in the salts arising from the combination of a weak base and a relatively

---

[1] A compound derived from dimethyl pyrone, in which the oxygen atom is in ternary oxonium combination, can be obtained by the action of dimethyl sulphate on the pyrone. To compounds of this type Kehrmann naturally assigned structure I (A=acid radical), but Baeyer (*Ber.* 1910, **43**, 2337) has

strong acid, in that they exhibit the phenomenon of hydrolytic dissociation, and consequently give a strong acid reaction in aqueous solution. The hydrolysis is not, however, complete in the case of a moderately concentrated solution of dimethyl pyrone picrate, for Walden in 1901 compared the partition coefficient of picric acid between benzene and water both with and without the addition of dimethyl pyrone, and found that the ratio

$$\frac{\text{Concentration of benzene solution}}{\text{Concentration of aqueous solution}}$$

is less when the dimethyl pyrone is present, and so concludes that in the aqueous solution the pyrone exists in the form of a picrate. Other methods have also led to the same conclusion, thus from measurements of the depression of the freezing point of aqueous solutions of the hydrochloride, the amount of the depression obtained, if no compound existed in solution, should be equal to the sum of the depressions produced by the known amount of the pyrone and of hydrochloric acid present, whereas the actual values obtained are less than this sum. Again, if no compound were formed, the electrical conductivity of the solution should be the same as the conductivity of a solution of pure hydrochloric acid of the same concentration, but if any appreciable amount of the salt exists in solution this will of necessity give rise to a certain amount of $C_7H_8O_2.\overset{+}{H}$ ions and of Cl ions, which means that the number of hydrogen ions in the solution would be less than the number present in a solution of pure hydrochloric acid of the same concentration, and consequently the electric conductivity would be greatly reduced. Actual experiments

recently shown that structure II should be employed instead, since ammonia converts the compound in question into γ-methoxy-lutidine (III).

I   II   III
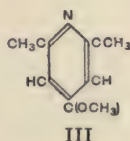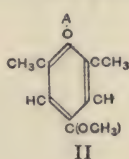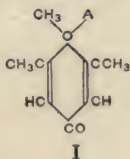
show that this is the case, and that the conductivity tends to decrease more and more as the solution becomes more concentrated.

Many instances may be given in which this idea of oxonium salts offers an explanation of observed facts. Thus Brühl in 1897 drew attention to the fact that the observed molecular refraction in the case of hydrogen peroxide is much greater than the calculated value, and advocated the quadrivalency of oxygen both in the peroxide and also in water, the two compounds being represented as shown :—

$$\begin{matrix} H-O-H \\ \| \\ O \end{matrix} \quad \text{and} \quad \begin{matrix} H-O-H \\ \| \\ H-O-H \end{matrix}$$
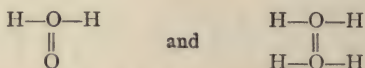
It has been known for many years that the colourless xanthydrol dissolves in hydrochloric or sulphuric acid to form a yellow solution, showing a strong green fluorescence, a result which may be explained on the assumption—
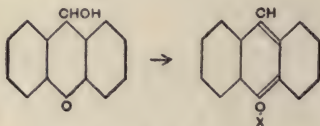
Confirmation of this is given by Werner's isolation of the ferrichlorides of compounds of such types, and by Hewitt's preparation of the salts of fluoran and fluorescein with mineral acids, whilst a similar type of reaction may be seen in the case of xanthone derivatives, thus—

Colourless   Yellow
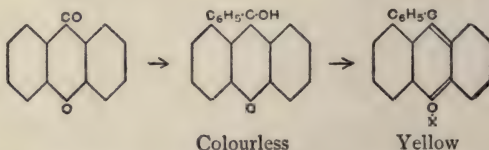
a condition in this latter case which may possibly be comparable with that obtaining in the acridine series.
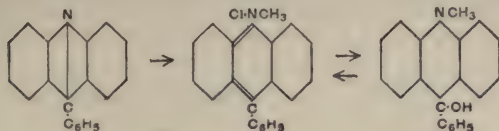
Baeyer and Villiger in 1901 and 1902 made an exhaustive examination of many substances in which the possibility of quadrivalent oxygen was existent, and isolated and examined compounds of ethers, alcohols, acids, esters, aldehydes, and ketones, with oxalic, ferrocyanic, ferricyanic, chlorplatinic, and other acids, and have in all cases explained in a satisfactory manner their results, by the assumption of the quadrivalency of oxygen. Walker and his co-workers have found that many organic substances containing oxygen and nitrogen dissolved in the liquefied acids and yielded conducting solutions, and also that there was strong evidence in favour of the existence of additive compounds, facts which can receive a satisfactory explanation in the case of nitrogen on the assumption of change from the tervalent to pentavalent condition, whilst a similar explanation of change of valency could be given in the case of oxygen. Archibald and M'Intosh have obtained definite compounds of hydriodic acid with diethyl, methyl amyl, and phenyl methyl ethers, acetone, and ethyl and propyl alcohols. Hydrobromic acid forms similar compounds except in the case of ethyl alcohol, and hydrochloric acid also, except in the cases of methyl and propyl alcohols. These substances are all colourless crystalline compounds of definite melting point, and their structure is explained on the assumption that oxygen possesses valencies higher than that usually assigned to it. The following structural formulæ have been given to some of these products—

$$(CH_3)_2.C:O.H \qquad (CH_3)_2C:O.Br \qquad C_6H_5.\overset{\displaystyle H}{\underset{\displaystyle Br}{\overset{|}{\underset{|}{O}}}}.CH_3$$
$$(CH_3)_2.C:O.I \qquad\qquad\quad H$$
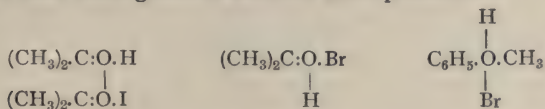
the authors assuming that the lower the temperature at which the erection is carried out the higher will be the valency of the oxygen atom. Further examples of the production of oxonium

salts are seen in the cases of the coeroxonium salts obtained by Decker from the action of fuming sulphuric acid on fluoran and its derivatives, these compounds dissolving in the acid with production of a yellow salt from which water is eliminated and a stable red salt is ultimately obtained.

Yellow.　　　Red.
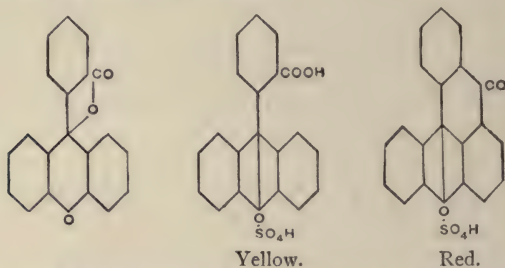
Perkin, in 1908, also obtained pyranol salts by the condensation of resorcinol and resorcylic aldehyde with ketones in the presence of hydrochloric acid, and found that they gave well-defined platini-chlorides and ferrichlorides.
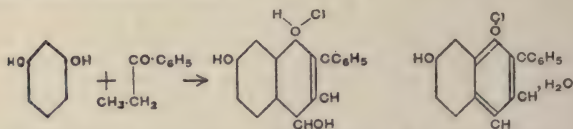
Finally, as further examples of oxonium salts may be mentioned the hydrochlorides of the hydroxyazo-compounds and their ethyl ethers, which have been prepared by Hewitt and his co-workers in recent years,

a structure which agrees with the colour changes noticed on dissolving the azophenols in acid, and with the results of nitration in the presence of concentrated sulphuric acid, the ordinary ortho-para law being obeyed, since the benzene nucleus in acetanilide and in the sulphate of benzene-azo-phenol may be considered as analogous.
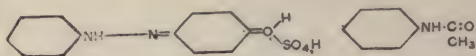
In some of the cases cited above, opposition has been brought forward to the oxonium salt theory, and a carbonium structure has been given to the salts. Baeyer, from a consideration of the salts of the triphenyl carbinol dyestuffs, came to the conclusion that their colour was due to an abnormality of one valency of the central carbon atom of the grouping, and he assumed that this bond differed essentially from the others, and was, in fact, an ionizing valency, thus $(CH_3O.C_6H_4)_3C.HSO_4$ was written as $(CH_3O.C_6H_4)_3.C\sim\sim\sim HSO_4$. This idea was extended by Silberrad to the case of octobromo-3.3^1-6.6^1-99^1-hexahydroxy-dixanthyl benzene tetracarboxylic acid, which was written as (I), and he concludes that such coloured substances can in nowise be regarded as quinonoid in type, the colour being due to the latent chromophoric action of the 9.9^1-xanthyl carbon atoms. It, however, seems strange that the analogy of the xanthyl group to the acridines should have escaped notice, and since the existence of quadrivalent oxygen is scarcely to be doubted after the work of Baeyer and Villiger and others, these xanthyl derivatives may perhaps thus be considered as quinonoid oxonium hydroxides (II).

(I)   (II)
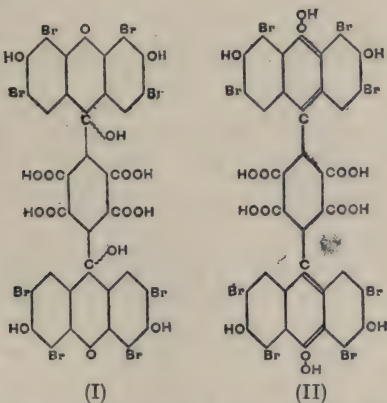
F. Baker has used the carbonium idea for the formulation of the salts of the azophenols and their ethers, but, as Hewitt points out, there are grave objections against such a structure which

involves nitrogen in a quinquevalent condition never before observed. The general formula of such salts is given by Baker as

and this has met with hostile criticism from Hewitt and Fox, who indicate that it is not apparent whether Baker intends to represent the hydrochloride of benzeneazophenol as (I) or (II).

(I)   (II)
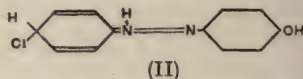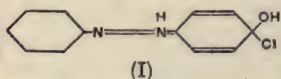
for a compound of structure (I) should not be so readily attacked by substituting agents, whilst against (II) may be urged the fact that the hydrochloride of p-bromobenzeneazophenol and the hydrobromide of p-chlorobenzeneazophenol are absolutely different, whereas such a structure would require them to be identical, viz. :—
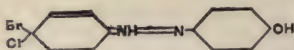
Gomberg also is in favour of the carbonium structure for the salts of the acridine series, which he writes as shewn,
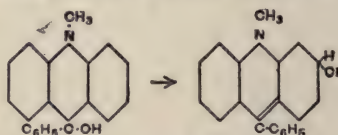
addition taking place on the carbon atom as against the nitrogen atom. If this view is accepted, then one should assume
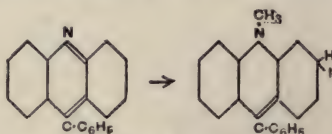
which seems to be counter to the general ideas of salt formation, for a common-sense point of view would indicate that in a stable

salt it seems obviously preferable to assume that the negative element is attached to the element capable of forming a strong base, so that if a choice is to be made between carbon and nitrogen then one would by preference attach the negative element to nitrogen. The same idea has also been extended to the xanthenols, the intensely coloured hydrochloride of the phenyl xanthenol being represented by the formula (I), but Kehrmann is of the opinion that this salt when heated passes with elimination of hydrogen chloride into the coloured oxonium chloride (II).
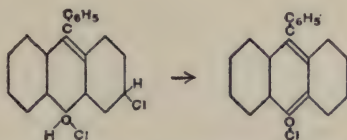
In order to account for the existence of certain types of compounds which do not contain hydrogen directly replaceable by metal, but which are capable of changing into a salt forming isomeride, Hantzsch, in 1899, introduced his conception of *pseudo-acids*. A well-known example of such a case is seen in phenylnitromethane, which, as ordinarily prepared, is a colourless liquid, soluble to a certain extent in water and without action upon ferric chloride solution. On treatment with sodium ethoxide it forms a sodium derivative, which, on acidification with dilute acid, passes into a solid form of the nitro-compound. This modification is relatively unstable, and, on keeping, gradually passes back again into the liquid form. The solid form is probably hydroxylic in structure, since its aqueous solution gives a red brown coloration on the addition of ferric chloride, whilst the substance itself also reacts with phenyl carbimide, phosphorus pentachloride, and benzoyl chloride. The two forms may thus be represented :—

(I) $C_6H_5CH_2NO_2$ and $C_6H_5CH:NO.OH$ (II)
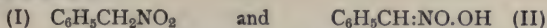
the sodium salt corresponding to (II), the iso-nitroso configuration. The liquid form, although it gives rise to a sodium derivative, is not, strictly speaking, an acid, but is designated by Hantzsch as a pseudo-acid (ψ-acid), and before it yields a

sodium salt it undergoes intramolecular rearrangement, yielding the isonitroso or true acid form. Again, the sodium salt, on treatment with a mineral acid, yields first the true acid or isonitroso-form, which, however, is unstable and gradually passes into the true nitro-compound or ψ-acid. The investigations of Hantzsch show that the following criteria may be used for the recognition of ψ-acids :—

(i) The compound is a ψ-acid if it *gradually* neutralizes an alkali. The ψ-acid as such does not neutralize the base, but on transformation into the true acid neutralization takes place, and of necessity, if the transformation is slow, then the process of neutralization must also be gradual. Again, if it is found that on decomposition of a solution of the salts with an equivalent quantity of a mineral acid, the electrical conductivity of the solution is considerably greater at first than after the lapse of some time, it indicates that the acid is a ψ-acid, the explanation being that the iso-form is a true acid, and is, therefore, a conductor in aqueous solution, whilst the solution of the normal modification is a non-conductor.

(ii) If the compound is neutral or only feebly acid, and yields salts which are neutral or feebly basic, that is, salts which are not hydrolytically dissociated, then it is a ψ-acid, and the salts are derived from a more strongly acid isomeride. In such a case a neutral solution of the salt mixed with an equivalent quantity of an acid remains neutral.

(iii) If the compound gives a colourless solution in ionizing solvents, but yields coloured salts and coloured ions in alkaline solution, then it is a ψ-acid.

(iv) An abnormally large temperature coefficient in the conductivity or dissociation constant of a solution, is an indication of the presence of a ψ-acid.

(v) If a substance does not combine directly with water or alcohol, but yields a stable hydrate or alcoholate by indirect methods, then it is a ψ-acid.

(vi) If a substance does not form a salt by direct combination with dry ammonia in a non-dissociating solvent (*e.g.* anhydrous-hydrocarbons), but does so in the presence of water, then the

substance is a ψ-acid. The formation of a salt, however, does not prove that the compound in question is a true acid.

The method of characterization of ψ-acids by the ammonia reaction is applicable when the following conditions are fulfilled :—

(a) The compound gives an ammonium salt in ionizing media.

(b) The ammonium salt is insoluble in non-ionizing liquids.

(c) The compound gives no precipitate of the ammonium salt on treatment with dry ammonia in the non-ionizing liquid.

As a rule it is merely necessary to see if the compound gives a precipitate of an ammonium salt in anhydrous ether solution, and if so, then it is a ψ-acid provided the salt is insoluble in benzene or chloroform. The method is of use for distinguishing between groups of isomeric and tautomeric substances and for detecting *ionization isomerism.*[1] The conclusion that all compounds which combine directly with ammonia, in benzene solution, are true acids, cannot be drawn, since a ψ-acid may undergo isomerism in the benzene solution, under the influence of the ammonia, and again, all enolic compounds yield ammonium salts in non-ionizing media.

Among the numerous compounds which behave as ψ-acids may be mentioned nitromethane and its mono and dibromo derivatives, phenyl-nitromethane (see above) and numerous other compounds, some typical examples of which are mentioned in the following context. *Isonitroso-acetone,* $CH_3COCH:N.OH$, is neutral to litmus and forms no compound with ammonia. The increase in conductivity of its sodium salt from dilution 32 to 1024 litres is only very little greater than that exhibited by salts of strong acids, and the sodium salt again is only very slightly hydrolyzed in aqueous solution. Hence the salt is perhaps to be considered as

$$CH_3.C(ONa):CH.NO \quad \text{or} \quad \begin{matrix} O-N.ONa \\ | \quad | \\ CH_3C=CH \end{matrix} \quad \text{or} \quad \begin{matrix} O-N \\ | \quad \| \\ CH_3(ONa)C-CH \end{matrix}$$

---
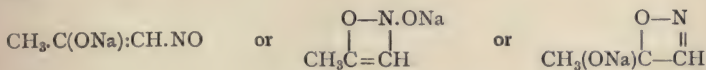
[1] When the salt-forming modification of a substance is not known in the free state, but only in solution (or as an ion in aqueous solution), Hantzsch describes the case as one of *ionization isomerism.*

Quinone-oxime, $HON:C_6H_4:O$, is a ψ-acid, since it does not unite with ammonia, and the sodium salt shows the normal increase in conductivity, consequently this salt must be the salt of a strong acid. In aqueous solution quinone-oxime has an acid reaction and a large value for its dissociation (affinity) constant, and in very dilute aqueous solution possesses the same colour as equivalent solutions of the red sodium and green potassium salts. It would thus appear that the oxime undergoes partial transference in aqueous solution, and the case is one of ionization isomerism. On the other hand, the dioxime shows no appreciable conductivity, and the sodium salt is a true oxime salt, since it is largely hydrolyzed in aqueous solution.

Nitroform, $CH(NO_2)_3$, dissolves readily in solutions of caustic alkali, forming a yellow salt which does not undergo hydrolytic dissociation. On the addition of mineral acid to the solution a large electric conductivity is shown at first, but this gradually diminishes until it reaches the value due to that of the alkali ion and the mineral acid ion present in solution. The colour of the solution also disappears gradually, and the normal variety of nitroform may be extracted from the colourless solution.

$$HC(NO_2)_3 \xrightarrow{\text{KHO}} (NO_2)_2.C:NO.OK \xrightarrow{\text{HCl}} (NO_2)_2C:NO.OH$$

slowly changes
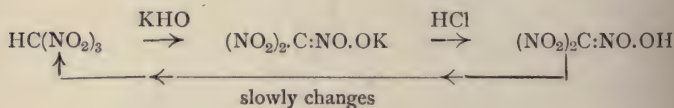
The *acid amides*, $R.CONHX$, are all ψ-acids, in the solid non-dissociated condition behaving as compounds $R.CONHX$, whereas their alkali salts possess the structure $RC(OM):NX$.[1] The true acids (isoamides) $RC(OH):NX$ have not yet been obtained in the solid state. The tendency of these ψ-acids to form salts with true acids increases with the negative character of the group $X(Cl,CN,NH_2)$.

The *nitro-amines*, $R.NH.NO_2$, are also ψ-acids and show a great tendency to undergo ionization isomerism.

The same idea may also be applied in the case of the phthaleins,

---

[1] M = metal.

thus in the case of phenolphthalein and its mono-sodium salt, which may be represented as
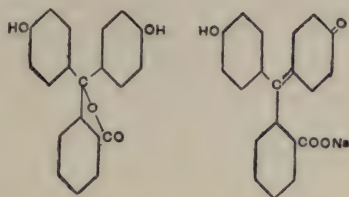
it is highly probable that the colourless free phenolphthalein is of the lactone type, whilst its highly-coloured sodium salt is quinonoid in structure, the free phenolphthalein thus behaving as a ψ-acid.

Similar considerations to those mentioned above may be extended to certain bases, and just as one can have ψ-acids, so the existence of ψ-bases may be assumed. These ψ-bases are neutral substances isomeric with the true ammonium hydroxides, and are capable, by the process of isomeric change, of passing into bases of the ammonium hydroxide type. Somewhat similar criteria are available for identifying such compounds, as were employed in the case of ψ-acids, the chief being :—

(i) The phenomenon of gradual neutralization, in which the conductivity of a mixture of a salt of the base and sodium hydroxide gradually decreases to that of the sodium salt produced, as the true base changes to the ψ-base.

(ii) Abnormal neutralization phenomena : where the velocity of change in (i) is too great to be observed, the neutral ammonium salt giving a neutral solution on the addition of one equivalent of alkali and the neutral ψ-base giving a neutral salt when mixed with one equivalent of acid.

(iii) The reluctance of the ψ-base to combine with an anhydrous acid or with an acid anhydride.

(iv) The formation of abnormal ethers and anhydrides.

As examples of ψ-bases may be mentioned *methyl phenyl acridinium hydroxide*, which was obtained by Bernthsen,
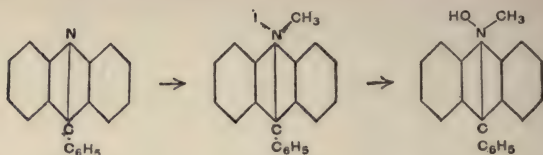
and was given the above constitution, corresponding to a quaternary ammonium base. The properties of the hydroxide do not, however, agree with the above structure, for such a compound should be a strong base, and should also dissolve in water and yield a strongly alkaline solution, whereas it is insoluble in water, and shows none of the properties associated with compounds of the type $R_4N.OH$. It is, on the other hand, soluble in hydrocarbon solvents, and behaves like a carbinol, so that Hantzsch considers it should be formulated as
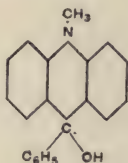
the true base (I), which is at first liberated when its salts are decomposed by alkali passing into the ψ-base (II). This is practically a non-electrolyte, as is shown by the fact that when a solution of the hydrochloride of the base is mixed with an equivalent quantity of sodium hydroxide solution, the solution possesses at first a maximum conductivity, which gradually diminishes until it reaches the value for a solution of sodium chloride of the same concentration.

(I)   →   (II)

True base ψ-base
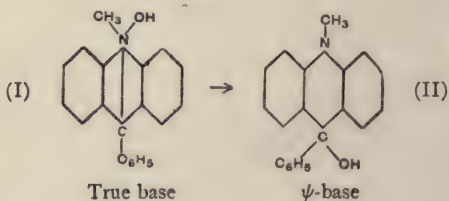
The values for the conductivity at 0° of a mixture of equal quantities of $\frac{1}{128}$N. solutions of the base and sodium hydroxide are given by the numbers—

On mixing	178.1
At 1 min. after mixing . . .	160.4
,, 30 ,, ,, ...	101.8
After 18 hours	61.6

The equivalent conductivity (*i.e.* conductivity ÷ concentration) of sodium chloride at dilution $v = 256$ is 61.1.

The above views of Hantzsch on the relation of quaternary ammonium salts to ψ-bases have received confirmation in the recent work of Tinkler, who has made spectroscopic examinations of acridine derivatives, and finds that acridine methiodide and acridine hydrochloride give practically identical absorption spectra, but that when caustic soda is added to an aqueous alcoholic solution of the methiodide, the absorption spectrum obtained closely resembles that of dihydroacridine.

Identical absorption spectra
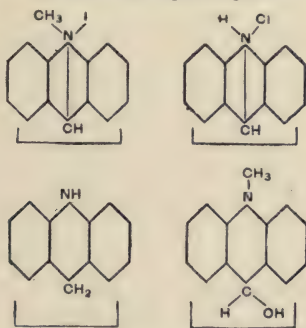
Identical absorption spectra, but
different from other pair

Similar changes have been observed with methyl acridine derivatives and also with phenanthridine methiodide and its hydroxide.

Similar absorption
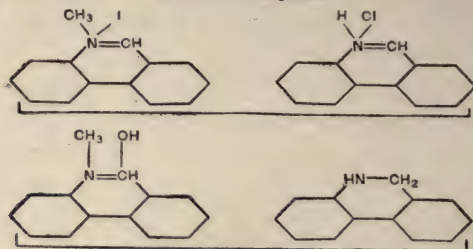
Similar absorption

Several interesting examples of ψ-bases are found among the dye-stuffs of the triphenylmethane series. Crystal violet (hexamethyl-pararosaniline chloride) $[(CH_3)_2N.C_6H_4]_2C : C_6H_4 : N(CH_3)_2Cl$ in solution, when mixed with an equivalent quantity of a base, at first still remains highly coloured, the solution being strongly alkaline, and conducting an electric current. After standing, however, for some hours the colour is gradually discharged, the alkalinity of the solution disappears, and it no longer conducts the electric current. The solution now contains the colour base which may be considered as a ψ-base of the carbinol type, the changes being represented :—

Colour salt   Labile true ammonium base

$$>C : C_6H_4 : NR_2Cl \quad \rightarrow \quad >C : C_6H_4 : NR_2.OH$$
$$\downarrow$$
$$>C(OH).C_6H_4NR_2$$

Colourless ψ-base
stable carbinol
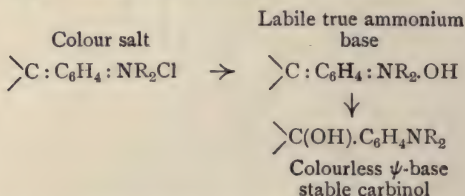
A similar condition appears to prevail among the triphenyl-methane dyes generally, thus *pararosaniline chloride*, $C_{19}H_{18}N_3Cl$, on treatment with alkali, yields the colourless base $C_{19}H_{19}N_3O$, which was recognized by E. and O. Fischer as being an ordinary carbinol base, and Rosenstiehl had suggested that the salts were consequently of the type $(H_2N.C_6H_4)_3C.Cl$, *i.e.* esters of a tertiary alcohol. This explanation does not, however, agree with the known facts, since on treatment with alkali the same phenomena

are observed as in the case of crystal violet, and a similar formu lation of the colour salt true base and ψ-base must hold.

Pararosaniline chloride

$$(H_2N.C_6H_4)_2C : C_6H_4 : NH_2Cl \rightarrow (H_2N.C_6H_4)_2C : C_6H_4 : NH_2OH$$

$$(H_2N.C_6H_4)_2.C(OH).C_6H_4NH_2$$
Pararosaniline
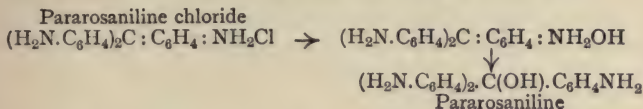
Considerable discussion has taken place as to the structure of the cyclic oxazine and thiazine dyestuffs, Hantzsch holding the view that they are paraquinonoid in structure and behave as quaternary ammonium salts, whilst Kehrmann looks upon them as orthoquinonoid oxonium and thionium salts. Kehrmann supports his views, as also in the case of the safranines, by the diazotizability of the amino-group, thus phenosafranine readily yields a chloride which may be either

(I) or (II)
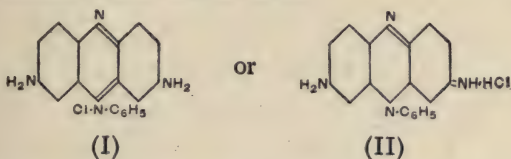
and this, when diazotized and boiled with alcohol, is converted into aposafranine, which may thus be

(III) or (IV)
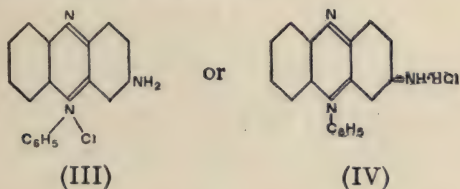
Since, however, aposafranine could be diazotized in the presence of concentrated sulphuric acid, and nitrogen eliminated from the product by boiling with alcohol (the addition of ferric chloride then salting out phenylphenazonium ferrichloride), Kehrmann concluded that a free amino-group is present in aposafranine, which is consequently to be represented by (III), thus necessitating the chloride of phenosafranine being (I). The corresponding

16

formulæ for hydroxyaposafranone, which had earlier been obtained by Nietzki and Otto, are
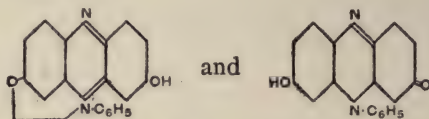
the former being favoured by Kehrmann. This would, however, lead to aposafranone being an internal salt of phenolic and quaternary ammonium functions, a conclusion in many respects at variance with facts, for such a compound should add on the elements of water and yield a strongly basic ammonium hydroxide, a result not realizable in practice.

Since the azo-compounds obtained from the cyclic thiazine series are of the type

$$\begin{array}{c} NH-C_6H_4 \\ | \qquad | \\ R.N:N.C_6H_4 - SO \end{array}$$
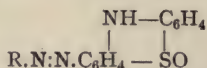
Hantzsch argues that the addition of water is a necessary preliminary to the possibility of diazotization, and that a quaternary ammonium salt type with paraquinonoid structure is present. He points out also that the salts of type

$$\begin{array}{ccc} Ar=N & & Ar=N \\ \| \quad | & \text{and} & \| \quad | \\ XO-C_6H_4 & & XS-C_6H_4 \end{array}$$

which Kehrmann views as the parent substances of Meldola's blue and methylene blue, are the salts of very weak bases, and are hydrolytically dissociated by water, whilst Meldola's blue and methylene blue are stable salts, the chlorides of Lauth's violet and Meldola's blue showing no more hydrolytic dissociation than does ammonium chloride. The addition of alkali brings about rapid and radical change in the base of Meldola's blue, whilst the hydroxyl base of Lauth's violet seems to have a transient existence, then passing into an anhydro-base,
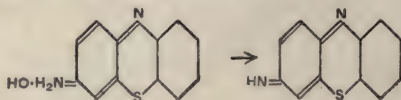
methylene blue giving a more stable base, the addition of one equivalent of alkali only leading to a *gradual* decrease of electrical conductivity which is probably due to gradual absorption of carbon dioxide from the air, the base undergoing autocatalysis into methylene azure.

The theory developed by Hantzsch regarding the existence of ψ-acids and bases cannot be perhaps accepted in its entirety, for it necessitates the idea of ψ-acids and bases being characterized by the hydrolysis of their salts in aqueous solution giving abnormal values. Undoubtedly this relation is proved experimentally in a large number of cases, but it hardly accords with the relation expressed by the simple equilibrium equation—

$$\text{Acid} \quad \rightleftharpoons \quad \psi\text{-acid,}$$

and, as Kauffmann has pointed out, a consistent application of the theory of electrolytic dissociation to the problem leads to the conclusion that the hydrolysis of salts of the ψ-acid should be normal. v. Zawidski has assumed that the abnormal behaviour of ψ-acids is accounted for by the supposition that they may be amphoteric electrolytes.

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THE PYRONES

THE pyrones are a series of six-membered heterocyclic ring compounds which may be considered as the anhydrides of diolefine-δ-hydroxylactonic acids, or as the anhydrides of diolefine dihydroxy-ketones. The former are known as the α-pyrones, the latter the γ-pyrones, corresponding respectively to the formulæ—

$$
\begin{array}{cc}
\overset{6}{\underset{5}{CH}} - \overset{1}{O} - \overset{2}{CO} & \overset{6}{\underset{5}{CH}} - \overset{1}{O} - \overset{2}{CH} \\
\overset{\shortparallel}{CH} - \overset{4}{CH} = \overset{3}{CH} & \overset{\shortparallel}{CH} - \overset{4}{CO} - \overset{3}{CH} \\
\alpha\text{-Pyrone} & \gamma\text{-Pyrone}
\end{array}
$$
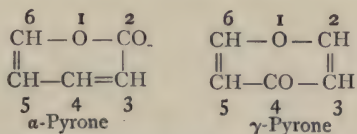
the attached numerals indicating the positions assumed by substituents. In the pyrone series the oxygen ring member is readily replaced by the equivalent imino-group (:NH), when these compounds are digested with ammonia, and in this way the pyridones (hydroxy-pyridine derivatives) are obtained.

α-Pyrone, $C_5H_4O_2$, is obtained by the distillation of the mercury salt of coumalic acid (α-pyrone-5-carboxylic acid) and is a crystalline solid. It is readily decomposed by the action of caustic alkali, ring fission taking place in the 1:2 position with production of an unsaturated hydroxy-acid, which, however, rearranges itself to form the more stable formyl crotonic acid.

$$
\begin{array}{ccc}
\begin{array}{c}
CH - CO \\
\shortparallel \quad | \\
CH \quad O \\
| \quad | \\
CH = CH
\end{array}
& \rightarrow &
\left[
\begin{array}{c}
CH.COOH \\
\shortparallel \\
CH \\
| \\
CH:CHOH
\end{array}
\right]
& \rightarrow &
\begin{array}{c}
CH.COOH \\
\shortparallel \\
CH \\
| \\
CH_2CHO
\end{array}
\end{array}
$$
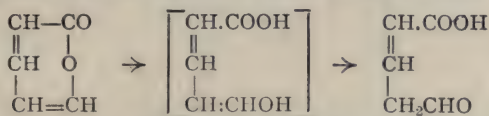
Coumalic acid is produced when malic acid is treated with fuming sulphuric acid to 100° C., and it may be assumed in this reaction that the first stage of the change consists in the elimi-

nation of carbon monoxide and of water from the malic acid, with the consequent production of hydroxy-methylene acetic acid, two molecules of this acid then reacting together to yield coumalic acid and water.

$$HOOC.CH_2.CHOH.COOH = CO + H_2O + HO.CH:CH.COOH$$

$$
\begin{array}{c}
HOOC.CH=CH \\
\quad | \\
\quad OH \\
HO.CH:CH.COOH
\end{array}
\rightarrow H_2O +
\begin{array}{c}
HOOC.C=\!\!=CH \\
\quad | \quad\ | \\
\quad CH \quad O \\
\quad \| \quad\ | \\
\quad CH-\!\!-CO
\end{array}
$$
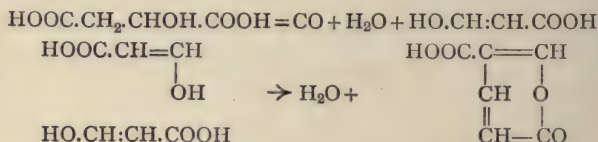
Coumalic acid is a crystalline solid and yields colourless crystalline salts. When boiled with baryta water it decomposes with formation of glutaconic and formic acids.

$$
\begin{array}{c}
HOOC.C=\!\!|\!\!=CH \\
\quad | \quad | \\
\quad CH \quad O \\
\quad \| \quad\ | \\
\quad CH-CO
\end{array}
+ 2H_2O =
\begin{array}{c}
HOOC.CH_2 \\
\quad | \\
\quad CH \\
\quad \| \\
\quad CH.COOH
\end{array}
+ HO.CHO
$$
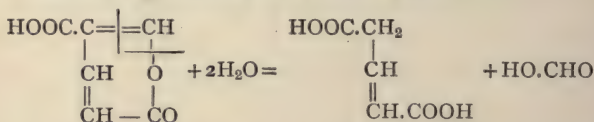
Dimethyl-coumalic acid (isodehydracetic acid), $C_8H_8O_4$, is an isomer of dehydracetic acid, and is obtained by the action of sulphuric acid on aceto-acetic ester, or by the condensation of sodium aceto-acetic ester with β-chloro-isocrotonic ester.

$$
\begin{array}{c}
ROOC.CH:C.CH_3 \\
\quad | \\
\quad OH \\
\\
\quad OH \\
\quad | \\
CH_3.C:CH.CO.OR
\end{array}
\rightarrow H_2O + R.OH +
\begin{array}{c}
ROOC.C=\!\!=C.CH_3 \\
\quad | \quad\quad | \\
CH_3.C \quad O \\
\quad \| \quad\ | \\
\quad CH-CO
\end{array}
$$

$$
\begin{array}{c}
ROOC.C=C.CH_3 \\
\quad | \quad\ | \\
\quad Na \ OH \\
\\
\quad Cl \\
\quad | \\
CH_3.C=CH.COOR
\end{array}
\rightarrow NaCl + R.OH +
\begin{array}{c}
ROOC.C=\!\!=C.CH_3 \\
\quad | \quad\quad | \\
CH_3.C \quad O \\
\quad \| \quad\ | \\
\quad CH-CO
\end{array}
$$
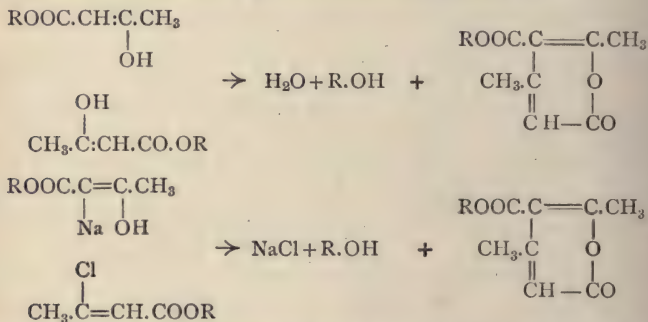
The free acid when heated to 240° C. loses carbon dioxide and is converted into dimethyl coumalin or mesitene lactone.

The most important of the α-pyrone derivatives, and certainly the one which has given rise to most discussion, is dehydracetic

acid, $C_8H_8O_4$, a compound first isolated in 1866 by Geuther, and which since then has been the subject of many investigations. Two alternative formulæ for the acid at present are in use, one due to Feist and the other to Collie. Each of these seems to answer fairly well with respect to the properties and reactions of the acid, and consequently a definite decision as to which is the more correct as yet seems impossible. The acid is thus represented as—

$$CH_3.C — O — CO$$
$$\overset{\|}{CH}—CO—CH.CO.CH_3$$

Feist's formula

$$CH_3COCH_2.C — O — CO$$
$$\overset{\|}{CH}—CO—CH_2$$

Collie's formula
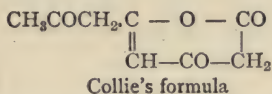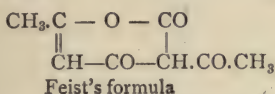
and is consequently a pyronone derivative. It is obtained by heating aceto-acetic ester alone, or with acetic anhydride at 200° C., or by heating acetyl chloride with pyridine. It yields crystalline salts and is very reactive. On hydrolysis with cold alcoholic potash it reverts to aceto-acetic ester, whilst if a hot concentrated solution be used, the products of hydrolysis are acetone, and carbonate and acetate of potassium. These reactions may be explained as follows :—

Synthesis (Feist)

$$CH_3.C.OH \quad ROOC$$
$$\overset{\|}{CH} \quad + \quad | \quad \rightarrow 2R.OH + $$
$$COOR \quad CH:C(OH).CH_3$$

$$CH_3.C — O — CO$$
$$\overset{\|}{CH}—CO—CH.CO.CH_3$$

or (Collie)

$$CH_3.CO.CH_2.COOR + H.CH_2.CO.CH_2.COOR$$
$$\downarrow$$
$$R.OH + CH_3.CO.CH_2.CO.CH_2.CO.CH_2.COOR$$
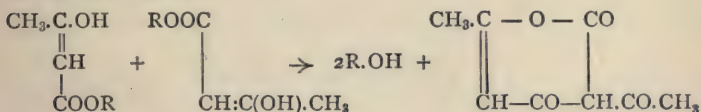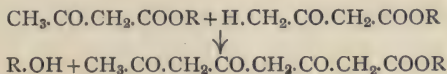
this ester now reacting in the enolic form and yielding the acid.

$$CH_3.CO.CH_2.C.OH \quad ROCO$$
$$\overset{\|}{CH}—CO—CH_2 \quad \rightarrow R.OH + $$

$$CH_3.COCH_2.C——O——CO$$
$$\overset{\|}{CH}—CO—CH_2$$
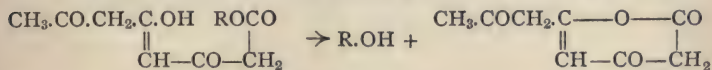
Since, however, a certain amount of ethylene is always simultaneously produced, it may be that this latter reaction takes the modified course—

$$CH_3.CO.CH_2\overset{O(C_2H_4)H}{\underset{O}{\overset{|}{C}}} \quad + \quad \overset{ROOC}{\underset{H_2CH.CO}{\overset{|}{CH_2}}}$$

$$= C_2H_4 + H_2O + R.OH + CH_3CO.CH_2.\overset{O——CO}{\underset{CH——CO}{\overset{|\quad\quad|}{C\quad\quad CH_2}}}$$

Hydrolysis (Feist)

$$2CH_3COCH_2COOH \quad \leftarrow \quad \overset{H\,|\,OH}{\underset{HO\,|\,H}{\overset{|}{CH_3.C——O—CO}}}\overset{}{\underset{CH—CO—CH.COCH_3}{}} \quad \text{or}$$

$$\overset{CH_3.C——O—|\,CO}{\underset{CH—CO—CH|COCH_3}{}} \quad \rightarrow \quad 2CH_3COOH + CO_2 + CH_3COCH_3$$

or (Collie)

$$\overset{CH_3.COCH_2.C——O—|—CO}{\underset{CH—CO—CH_2}{}} \rightarrow CH_3CO\,|CH_2.C(OH):CH.CO.CH_2.\,|COO|H$$

$$\downarrow$$
$$2CH_3COOH + CO_2 + CH_3COCH_3$$
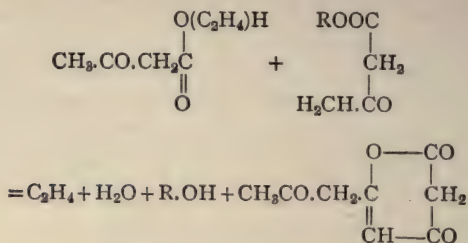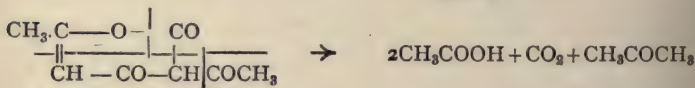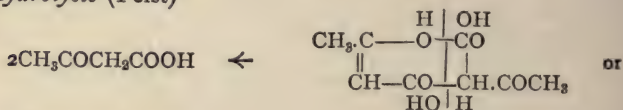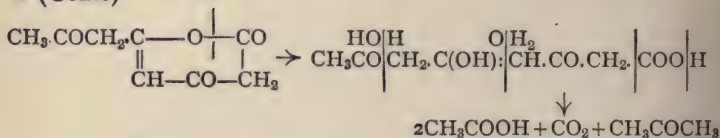
Collie's formula also explains the formation ot dehydracetic acid from acetyl chloride, more readily than that of Feist.

$$CH_3CO\big|Cl + H\big|CH_2.CO.\big|Cl + H\big|CH_2.CO\big|Cl + H\big|CH_2COCl\rightarrow$$
$$3HCl + CH_3CO(CH_2CO)_3Cl$$

$$\overset{CH_3.CO.CH_2.C:CH.CO.CH_2.CO}{\underset{O|H \qquad\qquad Cl|}{}} \rightarrow HCl + \overset{CH_3.CO.CH_2.C:CH.CO.CH_2}{\underset{O———CO}{}}$$
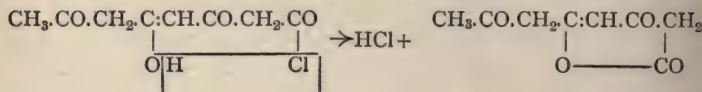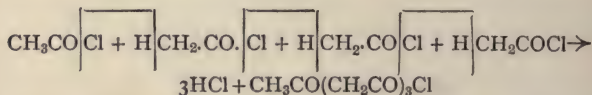
The acid reacts readily with ammonia to form pyridone derivatives, a result more easily explained on the Collie formula, although Feist has given a very ingenious interpretation to the reaction.

$$CH_3.C\text{——}O\text{——}CO$$
$$\overset{\|}{CH}\text{—}CO\text{—}CH.CO.CH_3$$
or

$$CH_3.C\text{——}O\text{——}CO$$
$$\overset{\|}{CH}\text{—}CO\text{—}C\text{:}C(OH).CH_3$$
$$\downarrow NH_3$$

$$CH_3.C.OH \quad COOH$$
$$\overset{\|}{CH}\text{—}CO\text{—}C\text{:}C(NH_2).CH_3$$

ring
fission
$\longleftarrow$

$$CH_3.C\text{——}O\text{——}CO$$
$$\overset{\|}{CH}\text{—}CO\text{—}C\text{:}C(NH_2).CH_3$$

or

$$CH_3.C.OH \quad HNH$$
$$\overset{\|}{\underset{CH\text{—}CO\text{—}C.COOH}{}} \overset{|}{\underset{}{C.CH_3}}$$
$\rightarrow$

$$CH_3.C\text{—}NH\text{—}C.CH_3$$
$$\overset{\|}{CH}\text{—}CO\text{—}\overset{\|}{CH}$$

or (Collie)

$$CH_3.CO.CH_2.C\text{:}CH.CO.CH_2.CO$$
$$\underset{O\text{————}}{|} \qquad |$$
or

$$CH_3.C(OH)\text{:}CH.C\text{:}CH.CO\cdot CH_2.CO$$
$$\underset{O\text{————}}{|} \qquad |$$
$$\downarrow NH_3$$

$$CH_3.C\text{:}CH.CO.CH\text{:}C.CH_2.COOH$$
$$\underset{NH_2}{|} \qquad \underset{OH}{|}$$
$\leftarrow$

$$CH_3.C\text{:}CH.C\text{:}CH.CO.CH_2.COOH$$
$$\underset{NH_2}{|} \underset{OH}{|}$$

$$CH_3.C\text{—}NH\text{—}C.CH_3$$
$$\overset{\|}{CH}\text{—}CO\text{—}\overset{\|}{CH}$$
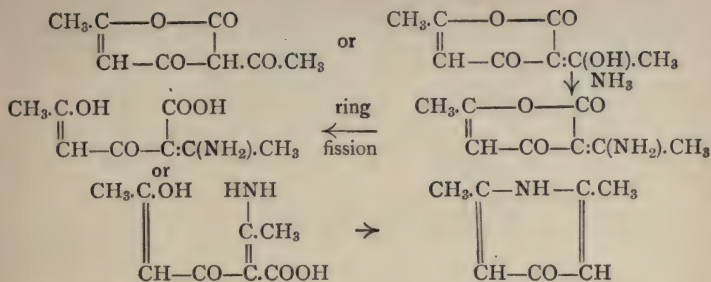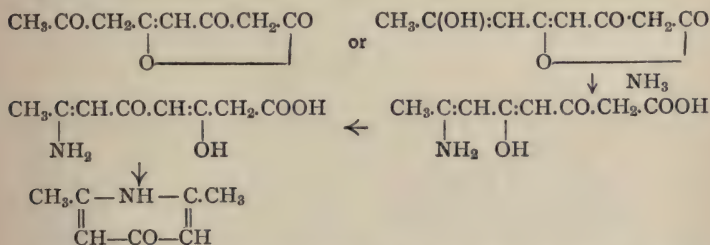
Dehydracetic acid on treatment with phosphorus pentachloride yields a dichloro-derivative, and on hydrolysis with caustic baryta yields orcinol, both reactions being readily explained by the Collie formula, but not by that of Feist.

$$CH_3.COCH_2.C\text{——}O\text{——}CO$$
$$\overset{\|}{CH}\text{—}CO\text{—}CH_2$$
$\rightarrow$

$$CH_3.C(OH)\text{:}CH.C\text{——}O\text{———}CO$$
$$\overset{\|}{CH}\text{—}C(OH)=CH$$
$$\downarrow$$
$$CH_3.C(Cl)\text{:}CH.C\text{——}O\text{——}CO$$
$$\overset{\|}{CH}\text{—}C(Cl)=CH$$

Baryta

$$CH_3.C(OH)\text{:}CH.C(OH)\text{:}CH.C(OH)\text{:}CH.COOH$$
$$\downarrow$$
$$CH\text{—}C(CH_3)=CH$$
$$HO.\overset{\|}{C}\text{——}CH=\!\!=\!\!=C.OH$$
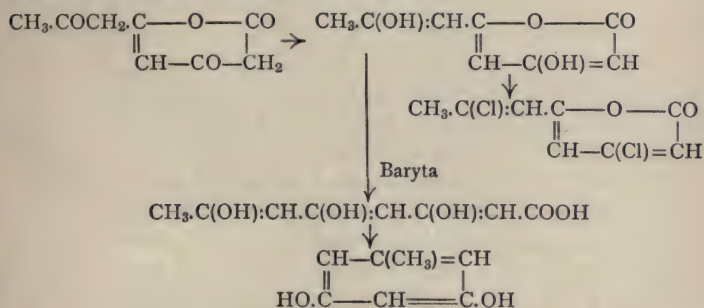
The production of triacetic lactone by heating dehydracetic acid with 90 per cent. sulphuric acid at 130° C. is readily explained by both formulæ.

$$CH_3.C\text{——}O\text{——}CO$$
$$\underset{CH\text{—}CO\text{—}CH.CO.CH_3}{\|}$$

$\rightarrow$

$$CH_3.C : CH.CO.CH.COCH_3$$
$$\underset{OH}{|} \quad \underset{HOCO}{|}$$

$$CH_3.C:CH.CO.CH_2$$
$$\underset{O\text{————}CO}{|\qquad\quad|}$$

↑ Lactonizes

$$CH_3.C:CH.CO.CH_2.CO$$
$$\underset{OH}{|} \qquad \underset{OH}{|}$$

↑ Rearrangement

or

$$CH_3.CO.CH_2.C\text{——}O\text{——}CO$$
$$\underset{CH\text{—}CO\text{—}CH_2}{|}$$

$\rightarrow$

$$CH_3.CO.CH_2.C:CH.CO.CH_2.COOH$$
$$\underset{OH}{|}$$
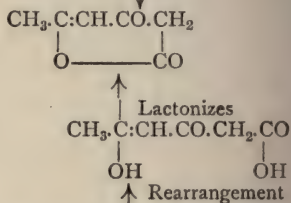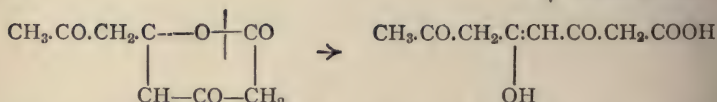
The triacetic lactone formed in this reaction, on treatment with excess of sulphuric acid is decomposed with production of acetyl acetone, whilst on hydrolysis by caustic alkali it yields acetone and alkali carbonate and acetate.

$$CH_3.C:CH.CO.CH_2$$
$$\underset{O\text{————}CO}{|\qquad\quad|}$$

acid or alkali →

$$CH_3.C:CH.CO.CH_2$$
$$\underset{OH}{|} \qquad \underset{COOH}{|}$$

↓ Acid
$$CO_2 + CH_3.CO.CH_2.CO.CH_3$$

↓ Alkali
$$CH_3COOH + CH_3COCH_3 + CO_2$$
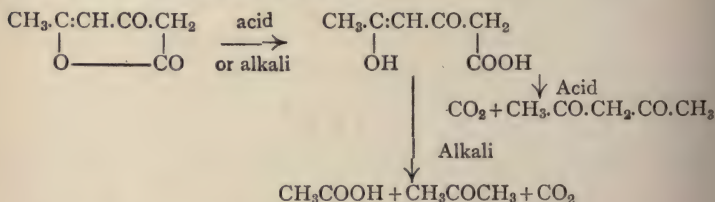
In 1907 Collie found that if the strength of the sulphuric acid used in the above reaction be reduced to 85 per cent., the yield of the triacetic lactone is diminished, but a compound, $C_8H_8O_4$, is obtained. This compound, when heated to 200° C. or with hydrochloric acid, decomposes into carbon dioxide and dimethyl-pyrone, and also when hydrolyzed with caustic baryta yields malonic and acetic acids. The solution of the sodium salt of this compound when boiled for some time decomposes with production of dehydracetic acid, and its fission product diacetyl acetone. These reactions are explained by Collie in the following manner :—

$$CH_3.CO.CH_2.C - O - CO \quad \xrightarrow{Acid} \quad CH_3.C:CH.CO.CH:C.CH_2.COOH$$
$$\underset{CH-CO-CH_2}{\|} \quad \xrightarrow{Alkali}$$

$$CH_3.C - O - C.CH_2.COOH$$
$$\underset{CH-CO-CH}{\|} \quad \underset{}{\|}$$

2-methyl pyrone-6-acetic acid

$$CH_3.CO.CH_2.C(OH):CH.CO.CH_2.COOH$$
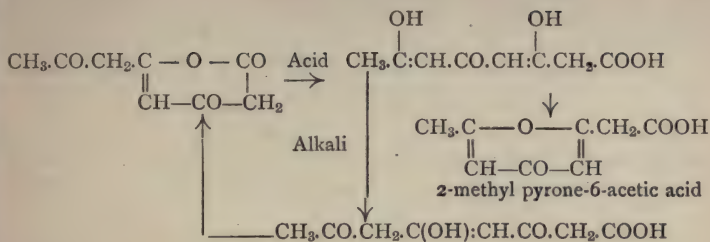
The formation of αα-dimethyl-γ-pyrone by the action of sulphuric acid on the dichloro-derivative of dehydracetic acid, followed by the heating of the resultant product, may also be readily explained on Collie's formula—

$$CH_3.C(Cl):CH.C - O - CO \quad \rightarrow \quad CH_3.C(OH):CH.C:CH.C:CH.COOH$$
$$\underset{CH-C(Cl)=CH}{\|} \qquad \qquad \underset{OH \quad OH}{\qquad}$$

or

$$CH_3.CO.CH_2.CO.CH_2.CO.CH_2.COOH$$

$$CH_3.C - O - C.CH_3 \qquad CH_3.C:CH.CO.CH:C.CH_2.COOH$$
$$\underset{CH-CO-CH}{\|} \quad \leftarrow \qquad \underset{OH \qquad\quad OH}{\qquad}$$
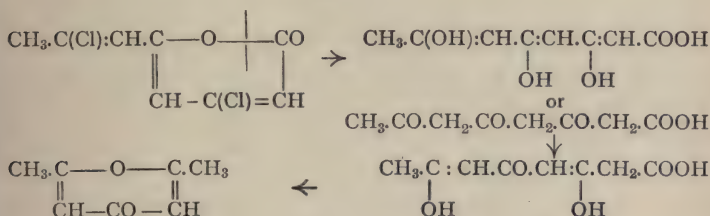
The formula for triacetic lactone given above has received confirmation at the hands of Tamburello and Carapelli, who have shown that it is converted by diazomethane into the corresponding methoxy-methyl pyrone.

Two series of benzo-α-pyrones are known, and are designated respectively as the coumarins and the isocoumarins.
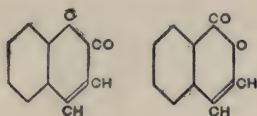
Coumarin, which is the odoriferous principle of the woodruff and of the tonka-bean, is prepared synthetically from salicylic aldehyde by the Perkin reaction,
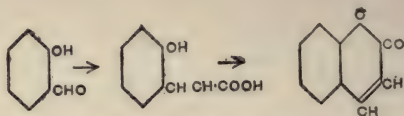
or, as von Pechmann has shown, by the condensation of malic acid with phenol in the presence of sulphuric acid.

$$\text{HOOC.CH}_2\text{.CHOH.COOH} \overset{\text{H}_2\text{SO}_4}{\rightarrow} \text{CO} + \text{H}_2\text{O} + \text{HO.CH:CH.COOH}$$
(Intermediate stage)
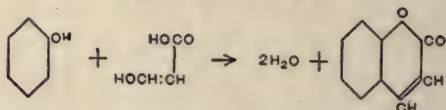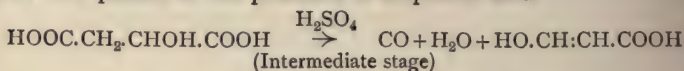
The homologous coumarins are similarly obtained by the condensation of phenols with aceto-acetic ester and substituted aceto-acetic esters, in the presence of sulphuric acid (v. Pechmann), or from the homologous (o)-hydroxyaldehydes by the Perkin reaction.
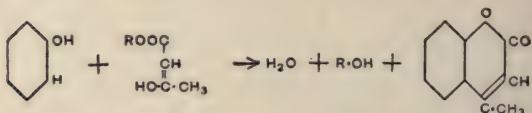
The isocoumarins have been prepared by Gabriel from the benzal or alkylidene phthalides. In this method of preparation the phthalides were converted into dinitro-derivatives either by the action of nitrous acid or by direct addition of nitrogen peroxide, and the nitro-derivatives so obtained were then heated, and finally reduced by hydriodic acid, when the isocoumarin was obtained.
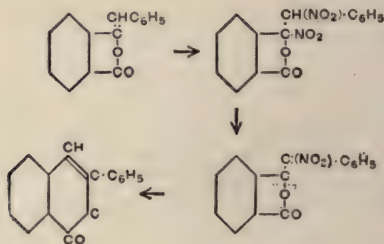
As an alternative method of preparation the acid anhydrides or chlorides may be heated with (o)-cyanobenzyl cyanide, the resulting nitrile being then hydrolyzed with acids.
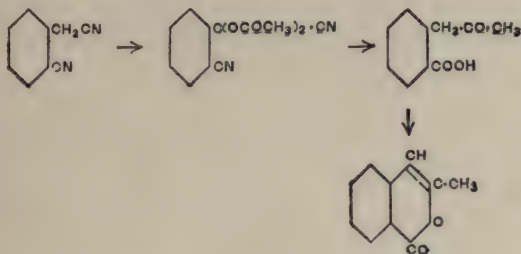
The γ-pyrones are the more important class of such compounds since many naturally occurring dyestuffs and other natural products are closely related to them. Ordinary opium readily yields meconic acid (3-hydroxy-γ-pyrone-2.6-dicarboxylic acid), and this acid when heated passes into comenic acid (3-hydroxyprone-6-carboxylic acid), and pyromeconic acid (3-hydroxy-γ-pyrone).
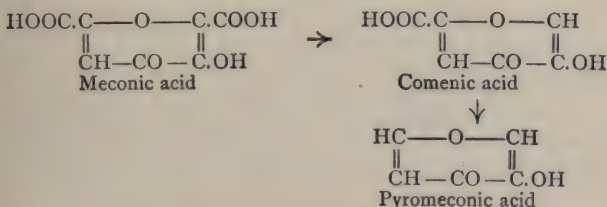
Chelidonic acid, $C_5H_4O_6$, is another naturally occurring pyrone derivative. It is found in the greater celandine (chelidonium majus), and has been synthesized from acetone and diethyl oxalate. These two compounds condense in the presence of sodium methoxide to form acetone dioxalic ester, which, when its alcoholic solution is boiled, immediately loses the elements of water and passes into the ethyl ester of chelidonic acid. Careful hydrolysis of this ester yields the free acid, and the latter, when heated, loses carbon dioxide and passes into the free γ-pyrone,

$$CH_3$$
$$|$$
$$CO \quad + 2ROOC.COOR \quad = \quad$$
$$|$$
$$CH_3$$

$$CH_2.CO.COOR$$
$$|$$
$$CO \qquad\qquad\qquad \text{or}$$
$$|$$
$$CH_2.CO.COOR$$

$$CH:C(OH).COOR$$
$$|$$
$$CO$$
$$|$$
$$CH:C(OH).COOR$$
$$\downarrow$$

$$CH=CH$$
$$|\qquad\ |$$
$$CO \quad O \qquad \leftarrow$$
$$|\qquad\ |$$
$$CH=CH$$
$$\gamma\text{-pyrone}$$

$$CH=C.COOH$$
$$|\qquad\quad\ |$$
$$CO \qquad O \qquad \leftarrow$$
$$|\qquad\quad\ |$$
$$CH=C.COOH$$
Chelidonic acid

$$CH=C.COOR$$
$$|\qquad\quad\ |$$
$$CO \qquad O$$
$$|\qquad\quad\ |$$
$$CH=C.COOR$$
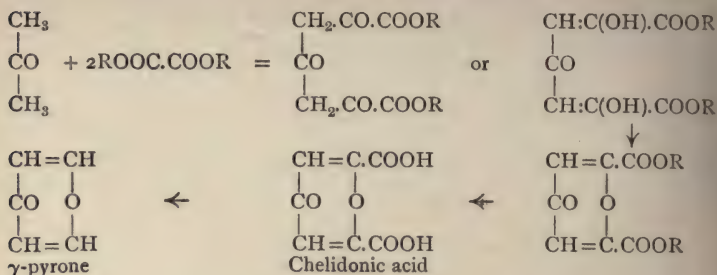
This acid yields colourless salts, but if it be warmed with an excess of alkali hydroxide, ring fission takes place, and the yellow salts of acetone-dioxalic acid (xantho-chelidonic acid) are produced. Xantho-chelidonic ester may also be synthesized by the condensation of oxalic ester with acetyl pyruvic ester in the presence of sodium ethoxide, the reaction taking place as shown.

$$CH_3.CO.CH_2.CO.COOR + ROOC.COOR = R.OH +$$
$$CO.[CH:C(OH).COOR]_2$$
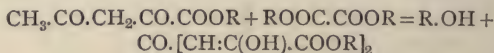
The most important of the γ-pyrones is $\alpha\alpha$-dimethyl-γ-pyrone, which, in the form of its hydrochloride, may be prepared by heating dehydracetic acid under pressure, followed by subsequent dehydration (over sulphuric acid) of the compound so formed. Feist concluded that the compound $C_7H_9O_2Cl$, formed in this manner, was a derivative of diacetyl-acetone and possessed the structure

$$CH_3.C(Cl):CH.CO.CH_2.CO.CH_3,$$
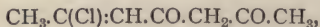
but Collie and Tickle showed that such a formula does not agree with the reactions exhibited by it, since it gives no colour with ferric chloride solution, and again on dissolving in water shows the behaviour of a mixture of dimethyl pyrone and hydrochloric acid (see p. 225), hence it is the hydrochloride of $\alpha\alpha$-dimethyl-γ-pyrone. It may also be prepared by the action of carbonyl chloride on the copper derivative of aceto-acetic ester, the resulting keto-ester being then hydrolyzed by sulphuric or hydrochloric acids.

ROOC.CH.CO.CH$_3$
|
Cu   + Cl$_2$OC=CuCl$_2$ +
|
ROOC.CH.CO.CH$_3$

ROOC.CH.CO.CH$_3$
|
CO
|
ROOC.CH.CO.CH$_3$

↓

HOOC.CH.CO.CH$_3$
|
CO
|
HOOC.CH.CO.CH$_3$

CH$_2$.CO.CH$_3$
|
CO $\xleftarrow{\;-\,CO_2\;}$
|
CH$_2$.CO.CH$_3$
Keto-form

↓

CH:C(CH$_3$)
| \OH
CO $\xrightarrow{\;-\,H_2O\;}$
| OH
| /
CH:C(CH$_3$)
Enol-form

CH=C.CH$_3$
| |
CO O
| |
CH=C.CH$_3$
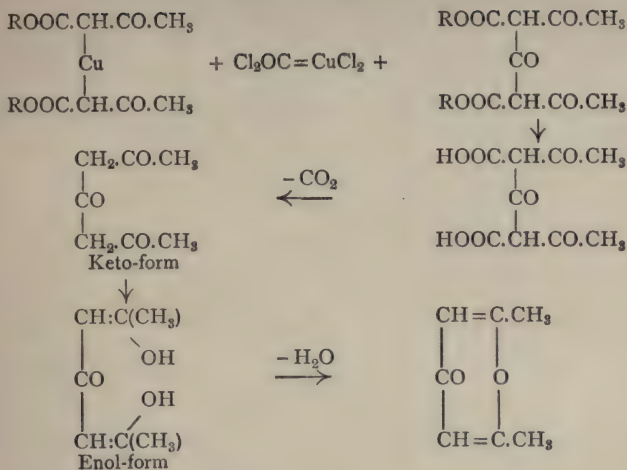
Dimethyl-γ-pyrone is characterized by the well-defined salts it yields with mineral acids (see p. 226). On hydrolysis with hot baryta water it yields diacetyl acetone,

$$CH_3CO.CH_2.CO.CH_2.COCH_3.$$

Numerous hydroxy-pyrones are known, and a certain amount of uncertainty as to the position of the hydroxyl group has arisen in various cases. An ingenious method has been devised by Peratoner for the determination of the position of the substituent in these cases, the *modus operandi* consisting in alkylating the hydroxy-compound by means of an aliphatic diazo-hydrocarbon and decomposing the resulting ether with baryta. In this way it is found that the ethyl ether of pyromeconic acid yields a formate and ethoxy-acetone, consequently pyromeconic acid must be 3-hydroxy-γ-pyrone.

HC—CO—C.OH   HC—CO—C.OC$_2$H$_5$
‖   ‖ →   ‖
HC—O—CH   HC—O—CH

↓ 3H$_2$O

2H$_2$CO$_2$ + CH$_3$.CO.CH$_2$OC$_2$H$_5$
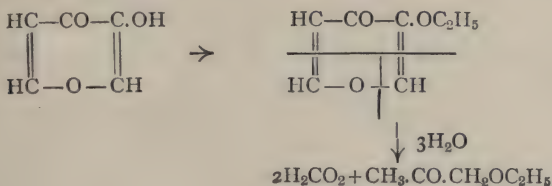
In the case of comenic acid the method will not distinguish between 3-hydroxypyrone-2-carboxylic acid and 3-hydroxypyrone-6-carboxylic acid, but a comparison of the dissociation constants of comenic acid and comanic acid (obtained by heating chelidonic acid)—

$$
\begin{array}{ccc}
HC\!-\!\!-\!CO\!-\!\!-\!CH & & HC\!-\!CO\!-\!CH \\
\| \quad\quad\quad \| & \rightarrow & \| \quad\quad\quad \| \\
HOOC.C\!-\!\!-\!O\!-\!\!-\!C.COOH & & HC\!-\!O\!-\!\!-\!C.COOH \\
\text{Chelidonic acid} & & \text{Comanic acid}
\end{array}
$$
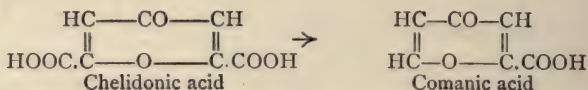
has shown that the latter is the stronger of the two. Since it has been shown that benzoic acid is a stronger acid than p-hydroxy benzoic acid, but a weaker acid than salicylic acid, it would appear by analogy, that in comenic acid the hydroxyl group should thus be in para-position to the carboxyl-group, that is, comenic acid should be 3-hydroxypyrone-6-carboxylic acid.

$$
\begin{array}{c}
HC\!-\!CO\!-\!C.OH \\
\| \quad\quad\quad \| \\
HOOC.C\!-\!\!-\!O\!-\!CH
\end{array}
$$
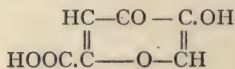
The method has also been used for the determination of the structure of maltol, which had earlier been formulated as—

$$
\begin{array}{c}
HC\!-\!CH\!-\!C.OH \\
\| \quad O \quad \| \\
| \\
HO.C\!-\!CH\!-\!CH
\end{array}
$$
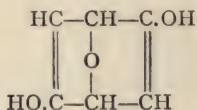
an unsatisfactory formula, since only mono-acyl derivatives are capable of preparation. Peratoner has found that on treatment with diazomethane it yields only a monomethyl ether, which on hydrolysis with baryta decomposes into formic and acetic acids and acetyl carbinol methyl ether. This decomposition can be represented in the following manner :—

$$
\begin{array}{ccc}
\text{(I)} & & \text{(II)} \\
CH_3O.C\!-\!CO\!-\!CH & & HC\!-\!CO\!-\!\!-\!C.OCH_3 \\
\| \quad\quad\quad \| & \text{or} & \| \quad\quad\quad \| \\
CH\!-\!O\!-\!C.CH_3 & & CH\!-\!O\!-\!\!-\!C.CH_3 \\
| & & |
\end{array}
$$
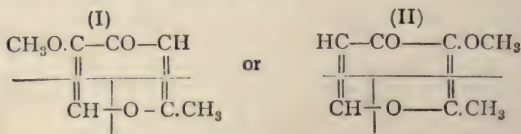
and of these formulæ (II) seems preferable, in that maltol differs

from its lower homologue (pyromeconic acid) in not reacting with amyl nitrite, diazonium salts or iodic acid.

Numerous benzo-γ-pyrones and dibenzo-γ-pyrones are known, the former including the naturally occurring products chrysine, apigenine, luteolin, etc., for the elucidation of the constitution of which we are indebted principally to the labours of Herzig, A. G. Perkin, and Kostanecki and his pupils; while the dibenzo-pyrones include xanthone and its chief derivatives, which have been examined by Kostanecki and also by Graebe.

The parent substance of the benzo-γ-pyrone group is *chroman*, $C_9H_{10}O$, which has been synthesized by J. v. Braun and Steindorff from tetrahydroquinoline. This quinoline compound is benzoylated, and the resulting benzoyl compound by the action of phosphorus pentachloride is converted into (*o*)-γ-chloropropylbenzanilide. The benzoyl group is now eliminated by hydrolysis and the amino-group in the so-formed chloropropylaniline replaced by the hydroxyl group in the usual manner. The phenol when boiled in alkaline solution passes quantitatively into chroman.
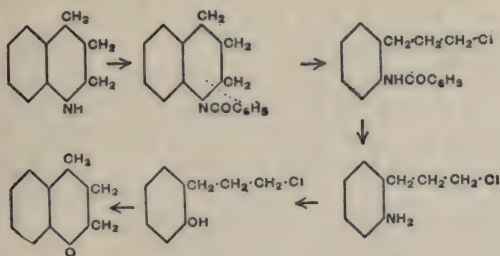
Chroman is thus obtained as a colourless strongly refractive liquid, boiling at 214-215° C., and having an odour of peppermint.

The benzo-γ-pyrones are consequently to be considered as chromones, such compounds being capable of synthesis, as Kostanecki has shown, by the condensation of (*o*)-hydroxyacetophenones with oxalic ester in the presence of sodium, the β-diketone which is formed passing into the chromone when its alcoholic solution is heated with hydrochloric acid.

17
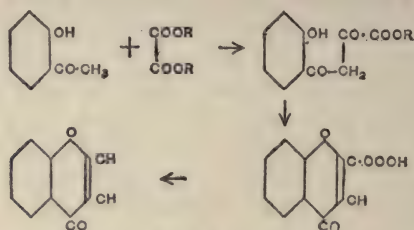
Benzo-γ-pyrone (chromone) has also been obtained by Ruhemann by the action of sulphuric acid on phenoxy-fumaric acid. In this reaction a benzo-γ-pyrone carboxylic acid is produced, and when heated in vacuo it loses carbon dioxide and is transformed into benzo-γ-pyrone.
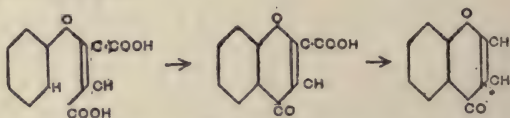
Chromone crystallizes in needles, melts at 59° C., and dissolves in concentrated sulphuric acid with a yellow colour, the solution exhibiting a blue fluorescence.

The naturally occurring yellow dyestuffs of this series are derivatives of flavone or 2-phenylbenzo-γ-pyrone, and flavonol. In the following pages the scheme of nomenclature outlined below is used, the numbers indicating the position of substituents.

Flavone
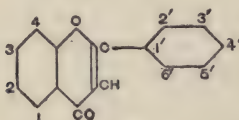
Flavonol
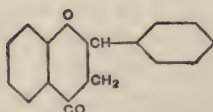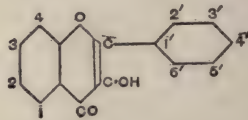
Flavanone
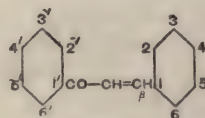
Chalkone

The chalkones are produced by the condensation of (*o*)-hydroxy-acetophenones and their derivatives, with aromatic aldehydes in the presence of the alkali hydroxides, thus :—

Resacetophenone   Methyl vanillin
ethyl ether
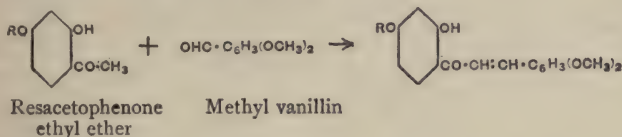
and when boiled with dilute sulphuric acid, pass, by ring closing, into the flavanones.
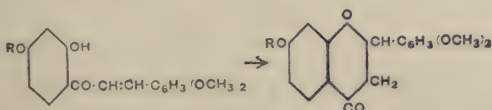
The flavanones are converted into flavonols by the action of amyl nitrite in acid solution, the isonitroso-compound first formed being decomposed by 10 per cent. sulphuric acid, and the resulting keto-compound finally reduced with hydriodic acid.
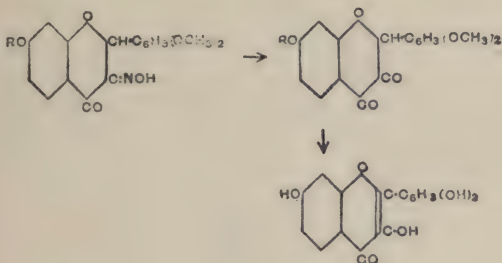
3.3′.4′-Trihydroxy flavonol
(Fisetin)

By similar processes the other members of the group are obtained, namely, chrysine, apigenine, luteoline, kæmpferol, quercitol, galangin, and morin, the starting point in each case being indicated in the subjoined t..ble.

NAME.	FORMULA.	STARTING POINT.
Chrysine	$C_{15}H_{10}O_4 = 1.3$ dihydroxy flavone	2'-Hydroxy-4'.6'-dimethoxy chalkone
Apigenine	$C_{15}H_{10}O_5 = 1.3.4$ trihydroxy flavone	2'-Hydroxy-4'.6'.4-trimethoxy chalkone
Luteoline	$C_{15}H_{10}O_6 = 1.3.3'.4$ tetrahydroxy flavone	2'-Hydroxy-4'.6'.3.4-tetramethoxy chalkone
Galangin	$C_{15}H_{10}O_5 = 1.3.$ dihydroxy flavonol	2'-Hydroxy-4'.6'-dimethoxy chalkone
Fisetin	$C_{15}H_{10}O_6 = 3.3'.4'$ trihydroxy flavonol	2'-Hydroxy-3.4.4'-trimethoxy chalkone
Kæmpferol	$C_{15}H_{10}O_6 = 1.3.4'$ trihydroxy flavonol	2'-Hydroxy-4.4'.6'-trimethoxy chalkone
Quercitol	$C_{15}H_{10}O_7 = 1.3.3'.4'$ tetrahydroxy flavonol	2'-Hydroxy-4'.6'.3.4-tetramethoxy chalkone
Morin	$C_{15}H_{10}O_7 = 1.3.2'.4'$ tetrahydroxy flavonol	2'-Hydroxy-4'.6'.2.4-tetramethoxy chalkone

In the case of the first three compounds above mentioned (namely, chrysine, apigenine, and luteoline) the synthesis follows slightly different lines from that given with the others, the flavanone being brominated (whereby three bromine atoms are introduced) and hydrobromic acid then removed from the bromo-compound by means of alcoholic potash. The resulting dibromo-flavanone on reduction with hydriodic acid yields the hydroxy-flavone.

1.3 Dimethoxyflavanone

Chrysine
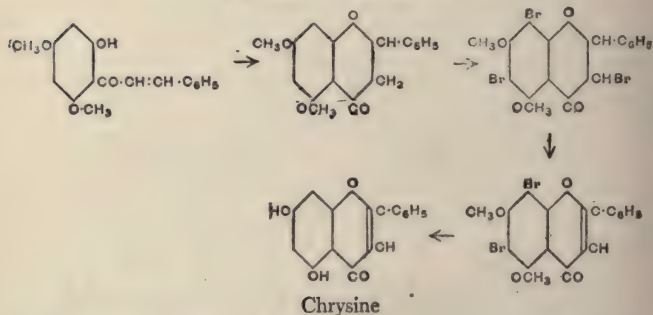
The reaction which supplied the clue rendering the synthesis of these compounds possible was their behaviour on fusion with

caustic alkali, whereby the polyhydric phenols were produced and generally an aromatic acid, examples being shown below.

$$C_{15}H_{10}O_4 + 3H_2O = C_6H_3(OH)_3 + C_6H_5COOH + CH_3COOH$$
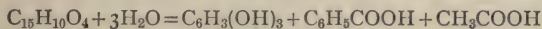
Chrysine   Phloroglucinol

$$C_{15}H_{10}O_6 + 3H_2O = C_6H_4(OH)_2 + C_6H_3(OH)_2 \cdot COOH + CH_2OH \cdot COOH$$
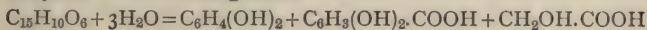
Fisetin   Resorcinol   Protocatechuic
                                     acid

Flavone itself was synthesized by Kostanecki from (*o*)-hydroxy-acetophenone and benzaldehyde. These two compounds condense together in alkaline solutions to form (*o*)-hydroxybenzal-acetophenone. The hydroxyl group of the ketone is protected by acetylation, the dibromo-addition product formed and finally converted into flavone by the action of alcoholic potash.
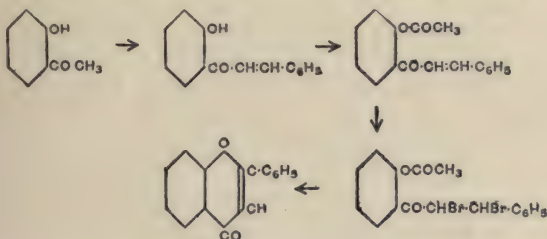
It dissolves in concentrated sulphuric acid, with a yellow colour and a weak blue fluorescence. The pyrone ring is readily broken by the action of the alkali hydroxides, the diketone first formed then undergoing further hydrolysis into (*o*)-hydroxyacetophenone and benzoic acid, together with salicylic acid and acetophenone.
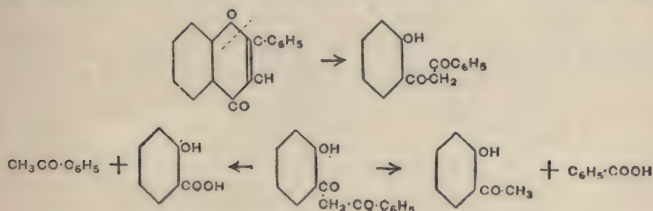
Among other substances closely related to the benzo-γ-pyrone group may be mentioned brazilin, $C_{16}H_{14}O_5$, and hæmatoxylin,

$C_{16}H_{14}O_6$, the colouring matters of Brazil wood and of logwood. Brazilin crystallizes in pale yellow prisms, and appears to have been first isolated by Chevreul in 1808. Somewhat later Kopp pointed out that it yielded resorcinol when distilled, or when fused with an alkali hydroxide. It contains four hydroxyl groups, since by the action of sodium methoxide it yields trimethyl-brazilin, a substance still containing a hydroxyl group, for, when heated in benzene solution at 120° C. with methyl iodide and sodium, it is further alkylated. These reactions show that three of the hydroxyl groups in brazilin possess phenolic properties, whilst the fourth is alcoholic in character. The oxidation of brazilin by drawing a current of air through its alkaline solution, gives an indication as to the structure of the molecule. In this reaction β-resorcylic acid and a dihydroxy-phenyl-γ-pyrone are obtained, the identity of the latter substance being confirmed by Feuerstein and Kostanecki, who showed that its dimethyl ether, on boiling with sodium ethoxide, yields fisetol dimethyl ether.
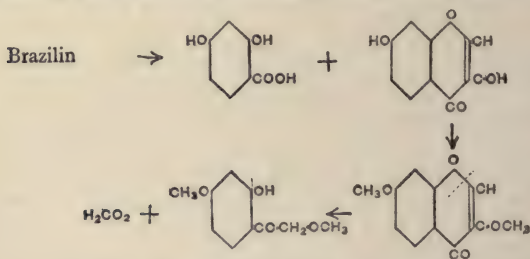
The constitution of brazilin has, however, been determined by W. H. Perkin in a series of investigations extending from 1901 to 1909, starting from the oxidation of trimethyl brazilin with potassium permanganate. In this oxidation, formic, acetic, and oxalic acids are produced, together with a series of acids of empirical formulæ.

$C_{19}H_{18}O_9$ = brazilinic acid.
$C_{10}H_{10}O_6$ = 2.carboxy-5-methoxy-phenoxyacetic acid.
$C_{10}H_{10}O_6$ = (m)-hemipinic acid.
$C_{12}H_{12}O_6$ = brazilic acid.

The formation of the phenoxy-acetic acid and of (m)-hemipinic

acid point to the presence of a resorcinol and a catechol nucleus in the molecule, and require the skeletal chains (I) and (II).

(I)   (II)
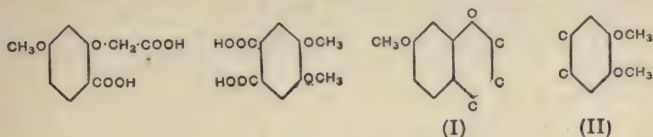
Perkin's earlier papers deal chiefly with the constitution of brazilic acid, from which the constitution of the brazilin itself is deduced. Brazilic acid, $C_{12}H_{12}O_6$, is a monobasic acid, but when boiled with baryta water yields a barium salt of composition $C_{12}H_{10}BaO_6$. The acid contains a methoxy-group (OCH_3) and a keto-group (CO), as shown by the Zeisel reaction, and by the formation of an oxime and a semi-carbazone. When fused with caustic alkali, it yields a water soluble acid, of which the aqueous solution gives an intense violet coloration on the addition of ferric chloride, a reaction pointing to the presence of a resorcyl nucleus. The carbonyl group is evidently in the γ-position, for the reduction of brazilic acid with sodium amalgam yields dihydrobrazilic acid, $C_{12}H_{14}O_6$, which, when liberated from its salts, immediately lactonizes. On treatment with concentrated sulphuric acid, brazilic acid passes into anhydrobrazilic acid, $C_{12}H_{10}O_5$, a monobasic acid which still contains the original methoxy-group and carbonyl group. The anhydro-acid is an unsaturated acid, since its solution in sodium carbonate at once decolorizes potassium permanganate, the product of oxidation being (p)-methoxy salicylic acid

$$CH_3O(5).C_6H_3.(OH).COOH(1.2).$$
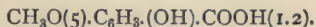
The anhydro-acid, on hydrolysis with caustic baryta, yields formic acid and a monobasic ketonic acid, $C_{11}H_{12}O_5$, which gives a violet coloration with ferric chloride.

$$C_{12}H_{10}O_5 + 2H_2O = C_{11}H_{12}O_5 + H_2CO_2.$$
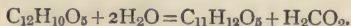
Since, however, anhydrobrazilic acid gives no coloration with ferric chloride, it is probable that the elimination of formic acid has been accompanied by the formation of a free hydroxyl-group in the benzene ring, a conclusion verified by the fact that the

methyl ester of the acid on alkylation yields the methyl ester of an acid, $C_{12}H_{14}O_5$, which gives no coloration with ferric chloride, so that the hydroxyl group in the former acid becomes the methoxy group in the latter. The general reactions of the acid, $C_{11}H_{12}O_5$, taken in conjunction with the oxidation of anhydro-brazilic acid to (p)-methoxy-salicylic acid point to it being 6-hydroxy-4-methoxy-benzoyl propionic acid.
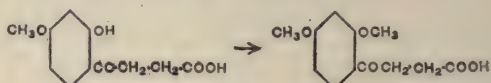
confirmation of which is found in the synthesis of the dimethoxy compound by the condensation of resorcinol dimethyl ether with the semi-chloride of succinic acid, in the presence of aluminium chloride.
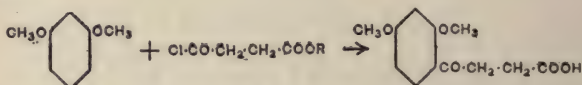
The formation of the acid $C_{11}H_{12}O_5$, and of formic acid, by the action of caustic baryta on anhydrobrazilic acid, is a type of reaction frequently met with in the benzo-γ-pyrone series, *e.g.* with fisetin,
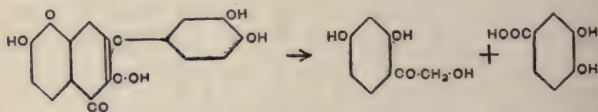
and by analogy it must be concluded that anhydrobrazilic acid is a γ-pyrone derivative of constitution.
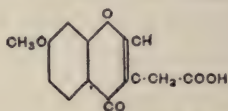
This structure has been confirmed by the synthesis of the acid from resorcinol dimethyl ether and succinyl chloride, which condense together in the presence of aluminium chloride (no solvent

being required) to form the acid $C_{11}H_{12}O_5$. The methyl ester of this acid, on treatment with ethyl formate in the presence of sodium, then yields a hydroxy-methylene derivative which passes by loss of water into anhydrobrazilic acid.
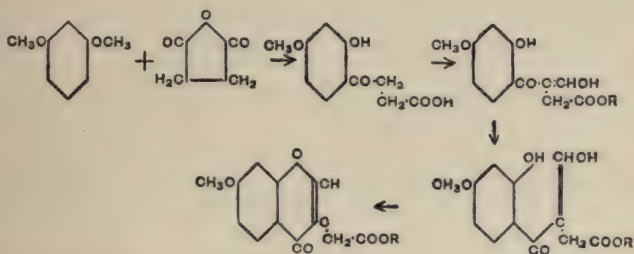
These results lead to brazilic acid being either
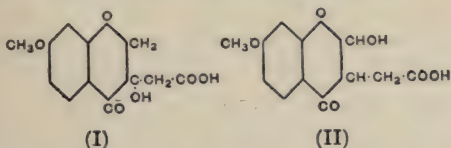
and of these only (II) could give a γ-lactone, but as brazilic acid is stable even when boiled with hydrochloric acid it must be (I).

Now, since the groupings
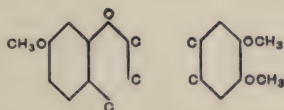
contain twenty carbon atoms and brazilin only contains nineteen, there must be one carbon atom in common, and this seems to be the one marked below
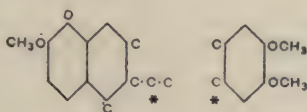
so that trimethyl brazilin and brazilin should apparently be represented as

Trimethyl brazilin
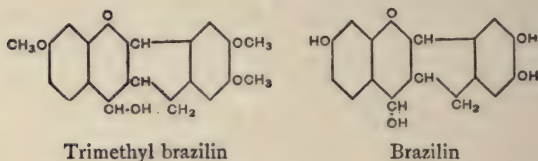
Brazilin

in order to account for the formation of brazilic acid, and of the presence of the three phenolic hydroxyl groups, the fourth being alcoholic in character.

In some respects the above formula did not seem satisfactory as a representation of brazilin, and further work was undertaken on brazilinic acid, which is formed in considerable quantity when trimethyl brazilin is oxidized with potassium permanganate. This acid, $C_{19}H_{18}O_9$, is dibasic, contains three methoxy groups, and on reduction with sodium amalgam yields a dihydro acid, which immediately lactonizes. The constitution of these acids was finally determined by their synthesis, brazilinic acid being formed in somewhat small yield by the condensation of (*m*)-hemipinic anhydride with the ethyl ester of (*m*)-methoxy phenoxy acetic acid in the presence of aluminium chloride.
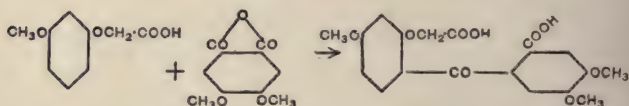
The lactone of dihydrobrazilinic acid arises in a similar fashion from (*m*)-hemipinic anhydride and resorcinol dimethyl ether, the pyrone derivative first formed being reduced by sodium amalgam, and the reduction product finally condensed with monochloro-acetic ester in the presence of alkali.

2¹-hydroxy-4.5.4¹-trimethoxy benzoyl benzoic acid

Lactone of dihydrobrazilinic acid   2-(*m*)-meconyl- 5-methoxy phenol
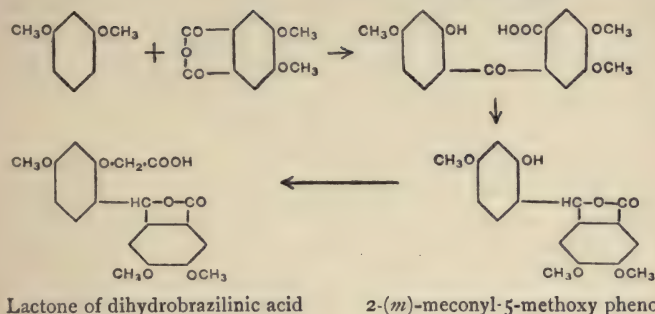
These syntheses require a slight alteration in the formula of brazilin, which must now consequently be written as
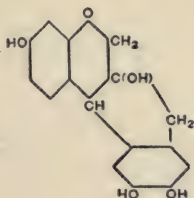
a configuration that allows for the formation of the four acids obtained when trimethyl brazilin is oxidized.

Hæmatoxylin is very similar to brazilin, yielding on fusion with alkali, pyrogallol. It contains five hydroxyl groups, one of which is alcoholic in character. Its tetramethyl derivative on oxidation yields among other products (*m*)-hemipinic acid, which points to the presence of a catechol nucleus, and thus the only point of difference between hæmatoxylin and brazilin seems to be that the former contains a pyrogallol and a catechol nucleus, whilst the latter contains a resorcinol and a catechol nucleus. Proceeding on lines similar to those used in the case of brazilin, hæmatoxylin must be represented by the following formula :—
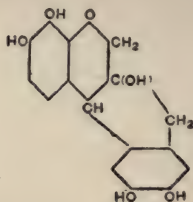
A similar series of synthetical reactions were carried out as in the case of brazilin, the lactone of dihydrohæmatoxylinic acid being prepared by the condensation of (*m*)-hemipinic anhydride with pyrogallol trimethyl ether.

The simplest of the dibenzo-γ-pyrones is xanthone, $C_{13}H_8O_2$, which was first obtained by Kolbe from the action of phosphorus oxychloride on sodium salicylate. It may also be obtained by the oxidation of xanthene with chromic acid, by distilling sodium salicylate with phenyl phosphate

$$3C_6H_4(OH).CO_2Na + PO(OC_6H_5)_3 = PO(ONa)_3 + 3H_2O + 3C_{13}H_8O_2$$
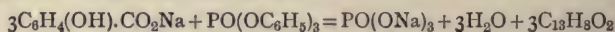
by the long continued boiling of salol,
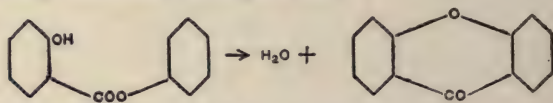
and by the dehydration of phenyl salicylic acid,
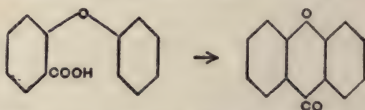
It is a crystalline solid. When distilled over zinc dust it passes into xanthene I (diphenylene methane oxide), whilst a less drastic reduction by means of zinc dust in the presence of an alcoholic solution of sodium hydroxide yields xanthydrol (II).
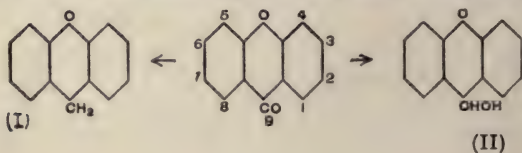
The position taken by substituents is indicated by the attached numbers in the xanthone formula. When heated with alcoholic potassium hydroxide at 180° C. it yields (o)-dihydroxybenzo-phenone, whilst an alkali fusion decomposes it into salicylic acid and phenol
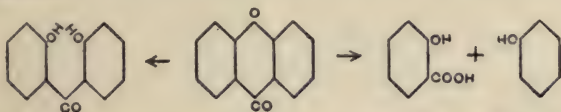
Numerous hydroxy-xanthones are known and are obtained by the condensation of (o)-hydroxy-carboxylic acids (e.g. salicylic acid, etc.) with phenols; thus from resorcinol the 1-hydroxy and 3-hydroxy-xanthones are obtained, whilst quinol yields 2-hydroxy-xanthone, and catechol, 4-hydroxy-xanthone.

and
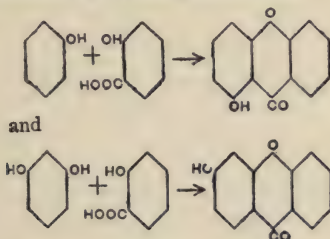
The most important of the dihydroxy-xanthones is the 1.7 compound or euxanthone which is obtained from Indian Yellow or Purree. Purree is obtained from the urine of cows which have been fed on mango leaves, and Graebe showed that it contains euxanthic acid (in the form of magnesium salt), $C_{19}H_{18}O_{10}$. This acid on hydrolysis yields euxanthone and glucuronic acid.

$$C_{19}H_{18}O_{10} + H_2O = C_{13}H_8O_4 + C_6H_{12}O_7$$
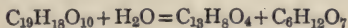
An examination of purree by Graebe showed that it contained,

Euxanthic acid,	. 51 %
Silica and alumina, .	. 1.5
Magnesium,	. 4.2
Calcium, .	. 3.4
Water and volatile matter,	39.0

the euxanthic acid and euxanthone being separated by rubbing it with dilute hydrochloric acid until the mass became bright yellow. The mass was then well washed and the free acid extracted by means of ammonium carbonate, whilst the residual euxanthone was extracted by sodium hydroxide and reprecipitated by the addition of acid.

Euxanthone was afterwards synthesized (by Graebe) by the condensation of β-resorcylic acid with quinol carboxylic acid, but this synthesis does not fix the position of the hydroxyl groups since there are two possibilities for the course of the reaction, namely,

and
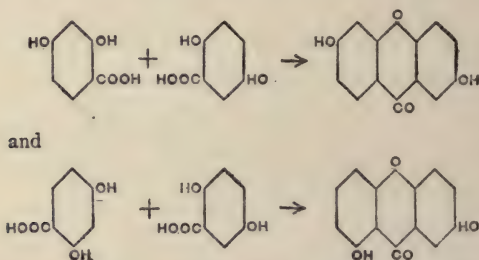
The constitution has, however, been definitely settled by Ullmann and Panchaud, who have shown that 2-chloro-6-methoxybenzoic acid condenses with quinol monomethyl ether in the presence of copper powder to 2-phenoxy-6-methoxy benzoic acid, which, when heated with concentrated sulphuric acid, yields euxanthone dimethyl ether.
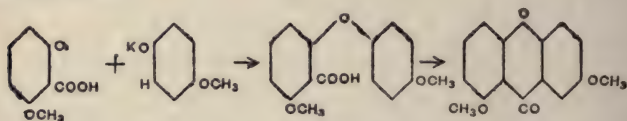
Euxanthone crystallizes in yellow needles and dissolves in solutions of the alkali hydroxides with a yellow colour.

Gentisin, $C_{14}H_{10}O_5$, and gentisein, $C_{13}H_8O_5$, which are found in the root of the gentian (*Gentiana luteola*) are trihydroxyxanthone derivatives. On alkali fusion, gentisin yields phloroglucinol, acetic acid, and quinol carboxylic acid. On methylation both

yield the same dimethyl ether, and so apparently gentisin is the monomethyl ether of gentisein. Kostanecki and Tambor have prepared gentisein synthetically by the condensation of phloro glucinol with quinol carboxylic acid in the presence of acetic anhydride.
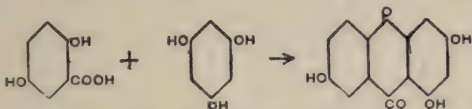
whilst gentisin is obtained by a similar reaction, using the mono-methyl ether of quinol carboxylic acid.
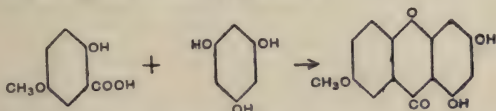
It is worth noting here that these compounds only yield dialkyl derivatives and not trialkyl compounds, for Kostanecki has shown that hydroxyxanthones with a hydroxyl group in the ortho-position to the CO group do not alkylate on this hydroxyl group.

Xanthene, $C_{13}H_{10}O$, the parent substance of the group, is not only obtained by the reduction of xanthone and of euxanthone, but is also produced when phenol is condensed with (o)-cresol in the presence of aluminium chloride. It is readily oxidized by chromic acid to xanthone. Various hydroxyxanthens have been obtained recently by the condensation of dihydroxybenzhydrols with phenols in the presence of zinc chloride.
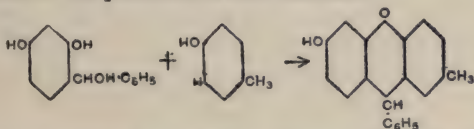
They are colourless solids which rapidly oxidize on exposure, becoming converted into the *fluorones*.
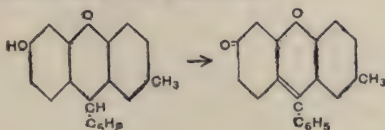
Compounds of the fluorone type were apparently first obtained by Möhlau and Koch in 1894 by the condensation of two molecular proportions of resorcinol with one molecular proportion of an aliphatic aldehyde in the presence of dilute (1:5) sulphuric acid, the resulting diphenylmethane derivative being then oxidized by heating with sulphuric acid. The hydroxyfluorones thus obtained were considered from their method of preparation to possess a para-quinonoid structure.
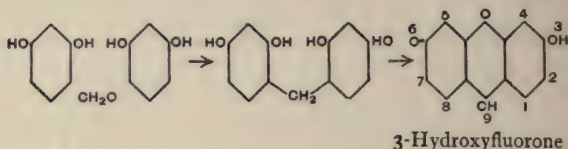
3-Hydroxyfluorone

In a somewhat similar manner, by using substituted phloroglucinols and hydroxyquinols in the presence of hydroxyaldehydes, numerous fluorone derivatives are obtained.

Kehrmann has recently prepared phenylfluorone and hydroxyphenylfluorone starting from acetyl-(*m*)-aminophenol and benzotrichloride, which, when heated together in nitrobenzene solution at 160° C., yield diacetylrosamine chloride and acetylaminophenylfluorone. The acetylaminofluorone is hydrolyzed and the amino-group diazotized, when hydroxyphenyl fluorone or phenylfluorone is produced, accordingly as the diazo-solution is boiled alone or with alcohol, thus :—
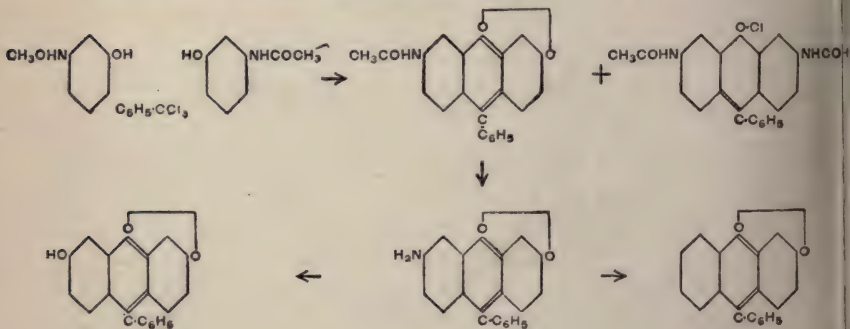
and in accordance with his well-known views, Kehrmann ascribes to these compounds the betaine type of orthoquinonoid structure.

This view of structure is combated by Decker, who has tried to prepare the analogue of phenyl fluorone from quinolphthalein by hydrolysis of 2-methoxy-9-phenylxanthonium bromide, but the only product obtained was a colourless carbinol base (I), namely, 2-hydroxy-9-phenylxanthen-9-ol, a reaction which shows that there is a fundamental difference between the two series, and hence phenyl fluorone must be represented by the formula (II)—

(I)   (II)
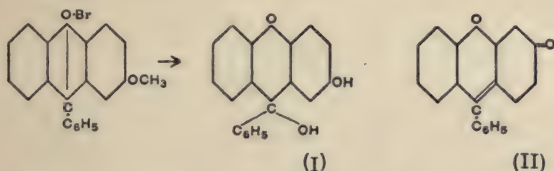
Again, Decker found that 3-methoxy-9-phenylxanthonium chloride, when heated with hydrochloric acid under pressure, yielded the corresponding hydroxy-compound, which was converted by sodium hydroxide into phenyl fluorone, the properties of the latter bearing no resemblance to those of a phenol-betaine, which should be soluble in water.
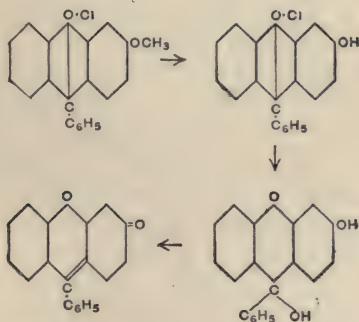
Pope and Howard have also prepared fluorones by the oxidation of hydroxyxanthens in alkaline solution, with a current of air,

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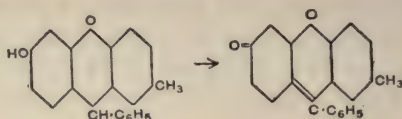
and find that the phenyl methyl fluorone obtained in this way is quite insoluble in water and in solutions of the alkali hydroxides, even when boiled; hence they conclude that the phenol-betaine formula of Kehrmann is untenable, and that (in agreement with Decker) the fluorones are paraquinonoid in structure.

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Kostanecki. Only the most important papers of this worker are given in the following list. From those given, references may be obtained to the earlier work.

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CHAPTER VIII

KETENS, OZONIDES, TRIPHENYLMETHYL

KETENS—The ketens are a series of unsaturated compounds containing the grouping $C:CO$, and may be considered as internal anhydrides of acetic acid and its substitution derivatives. The first member of the series was isolated by Staudinger in 1905, by the action of zinc upon a solution of α-bromoisobutyryl bromide in acetic acid.

$$(CH_3)_2.CBr.COBr + Zn = ZnBr_2 + (CH_3)_2C:CO.$$
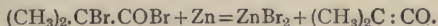
This dimethyl keten is a yellowish liquid that is stable at − 20° C., but at ordinary temperatures rapidly polymerizes to a compound which is probably a tetramethyl cyclobutane-dione.

$$\begin{array}{c} (CH_3)_2C\!\!-\!\!CO \\ |\quad\; | \\ OC\!\!-\!\!C(CH_3)_2 \end{array}$$
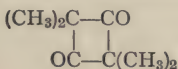
The ketens are usually prepared by the action of zinc filings on a solution of an α-halogen substituted acid chloride or bromide, in ether or ethyl acetate. In an examination of the relative merits of acid chlorides and bromides as starting-points for the preparation of ketens, Staudinger has found that α-bromo-acid bromides give the best results, but that if these are not available, then it is found to be preferable to employ an α-bromo-chloride rather than α-chloro-bromide, since the chlorine atom in the α-position is bound more tightly to the carbon atom than is the bromine atom in the α-position. In the case of diphenyl α-chloro-acetyl chloride it is found that this will readily react with zinc, although chloro-acetyl chloride will not, and the difference is explained by the assumption of the weakening effect of the two phenyl groups adjacent to the chlorine atom. Staudinger has tried the effect of replacing the metal zinc in these preparations by magnesium,

but although with bromo-acetyl bromide a good yield is apparent at first, so much hydrobromic acid is liberated towards the end of the reaction that the keten cannot be isolated.

The ketens are characterized by their additive reactions, combining readily with water to form acids, with alcohols to form esters, and with primary amines to form amides.

$$X_2C : CO + H_2O \quad \rightarrow \quad X_2CH.COOH$$
$$X_2C : CO + R.OH \quad \rightarrow \quad X_2CH.COOR$$
$$X_2C : CO + RNH_2 \quad \rightarrow \quad X_2CH.CONHR$$
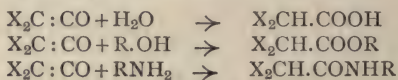
Two classes of ketens have been recognized, namely, the *keto-ketens*, $X_2C : CO$, which comprise the dialkyl or diaryl ketens, and the *aldo-ketens* $X.CH : CO$. The former are coloured compounds which readily undergo autoxidation, form keten bases on the addition of pyridine and quinoline, and combine with substances containing the $C : N$ and $C : O$ groupings, to form addition compounds. It is found that the Schiff's bases combine with two molecules of the keten, the combination taking place through the $C : N$ linking, and on this account the quinoline derivative of dimethyl keten is considered to be
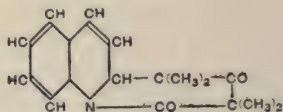
whilst the addition product with acridine possibly results by the fission of the para-linkage, the base having the annexed formula—
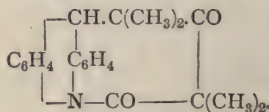
The products from the keto-ketens and Schiff's bases have apparently not yet been isolated in a pure condition, but are in all probability to be represented thus :—
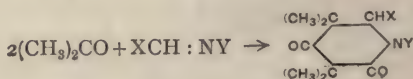
On the other hand, the aldo-ketens are colourless compounds which are not capable of autoxidation, are readily polymerized by pyridine and quinoline, and are inert towards substances containing the $C:N$ and $C:O$ groupings.

Wedekind has shown that the addition of a solution of iso-butyryl chloride in carbon bisulphide to trimethylamine or other fatty tertiary amine in the same solvent, yields dimethyl keten, which at once polymerises to 1.3-diketotetramethylcyclobutane,
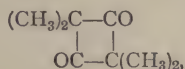
$$(CH_3)_2C——CO$$
$$OC——C(CH_3)_2,$$

whilst an addition product of composition $(CH_3)_2C:CO.NR_3$ is simultaneously formed. These latter products, which Wedekind designates as "ketenium" compounds, are obtained in larger yield if more of the tertiary amine be added as the reaction progresses. In the case of dimethyl keten and triethylamine, the dimethyl keten triethylium, $(CH_3)_2C:CO, N(C_2H_5)_3$, is isolated as a yellow oil of boiling-point 192° C., and possessing an odour like that of menthol. The compounds of this type differ from Staudinger's keten bases (1) in their very great stability, since they are not attacked by boiling dilute acid or alkali, or even by water at 160° C., whereas Staudinger's bases are decomposed by alkali; (2) in the relative proportion in which the constituent compounds unite to form the bases. Their reactions, as far as yet studied, apparently point to a cyclic structure, and the following formulæ have been proposed :—

$$R_2C————C:O \qquad R_2C————O$$
$$— NR_3 — \qquad — NR_3 —$$
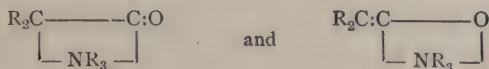
but it is as yet impossible to decide between the two alternatives.

Diethyl keten, $(C_2H_5)_2C:CO$, is obtained by heating diethyl-malonic anhydride, whilst diphenyl keten, $(C_6H_5)_2C:CO$, is prepared by the action of zinc on diphenyl-chloroacetyl chloride. The latter compound is an orange-red liquid which rapidly becomes viscid on exposure to air; it does not, however, polymerize. It

combines with benzoquinone, the resulting addition product being readily decomposed by heat.
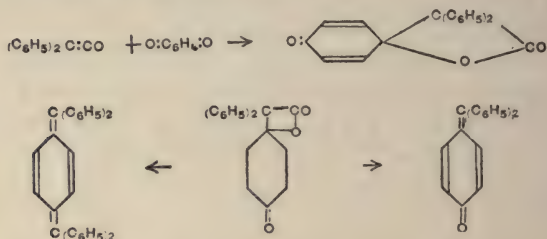
The addition product of diphenyl keten and dibenzylidene acetone is not stable, it loses carbon dioxide spontaneously, yielding 1.5-diphenyl-3-diphenylmethylene-1.4-pentadiene, a substance related to the fulvenes, but possessing less colour.

$$(C_6H_5)_2C:CO + CO(CH:CHC_6H_5)_2 \longrightarrow CO_2 + (C_6H_5)_2C:C(CH:CHC_6H_5)_2$$
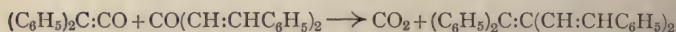
This appears, from some recent work of Staudinger's, to be a fairly general reaction, since experiments conducted with the quinoline derivative of diphenyl keten show that when heated with various carbonyl derivatives at 130° C. for 1.5 hours, reaction takes place in two stages, the first consisting in the formation of a β-lactone, which then splits up into carbon dioxide and an olefine derivative—

$$(C_6H_5)_2C:CO + R_2CO \longrightarrow \begin{matrix} R_2C\!-\!O \\ | \quad\ | \\ (C_6H_5)_2C\!-\!CO \end{matrix} \longrightarrow CO_2 + R_2C:C(C_6H_5)_2$$
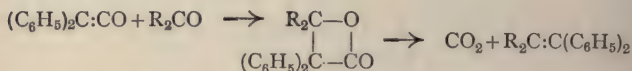
It is assumed that the second reaction proceeds with an incomparably greater velocity than the first. Among other results obtained it is shown that the reactivity of the keto-group is least when it is attached to an NR_2 or OR group (*i.e.* in carboxylic derivatives), more reactive when attached to H, CH_3 or C_6H_5, and most reactive when unsaturated groups (*e.g.* cyano, and cinnamenyl groups) are present. The following table shows the percentage amount of ketone entering into reaction with various carbonyl compounds :—

Carbonyl Cpd.	%	Carbonyl Cpd.	%
$R'.CO.CH:CHC_6H_5$	82.3	$R'.CO.OCOCH:CHC_6H_5$	5.3
$R'.COCN$	76.3	$R'.CO.OC_2H_5$	5.4
$R'.COH$	65.9	$R'.CON(C_6H_5)_2$	0.0
$R'.COC_6H_5$	42.5	$R''.COCH:CH.CH:CHC_6H_5$	85.7
$R'.COCH_3$	32.8	$R''.CO.C_6H_5$	55.6
$R'.COCl$	5.5	$R''.COCH_3$	20.7

(where $R' = C_6H_5CH:CH-$; $R'' = C_6H_5CH:CH.CH:CH-$)

Among other keto-ketens may be mentioned ethyl ethylketen carboxylate, $OC:C \overset{\textstyle COOC_2H_5}{\underset{\textstyle C_2H_5}{\big\langle}}$, which is obtained by the action of zinc on ethyl bromoethylmalonate chloride, and differs greatly from the other disubstituted ketens in being colourless and incapable of forming additive compounds. It rapidly polymerizes to 1.3-diethylcyclobutane-2.4-dione-1.3-dicarboxylate,

$$C_2H_5OOC.C(C_2H_5)\!-\!CO$$
$$OC\!-\!\!-\!\!-\!\!-\!\!-\!C(C_2H_5)COOC_2H_5$$
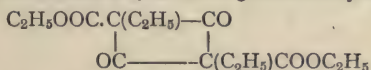
which, when heated to 180-200° C., depolymerizes and passes into the unimolecular keten.

Aldo-ketens may be prepared by methods similar to those used for the keto-ketens, thus methyl keten results from the action of zinc upon α-bromopropionyl bromide dissolved in ethyl acetate—

$$CH_3CHBrCOBr + Zn \longrightarrow ZnBr_2 + CH_3CH:CO.$$

The parent substance of the group, keten itself, $CH_2:CO$ (which may be regarded as an internal anhydride of acetic acid) was first obtained in 1907 by Wilsmore, among the gaseous products formed when a platinum wire is electrically heated under the surface of acetic anhydride; and subsequently by Staudinger, from the decomposition of bromo-acetyl bromide by means of zinc, the products of reaction being separated by fractional distillation. At ordinary temperature it is a colourless gas which may be condensed to a liquid (b.p. − 56°), and finally to a solid (m.p. − 151°).[1] It possesses a pungent odour, and its vapour

attacks the mucous membrane violently. Tertiary bases induce polymerization of keten, a similar condition arising if it be allowed to stand for some time, when a brown-coloured liquid is obtained. From this liquid Wilsmore isolated a compound which he considers to be acetyl keten, $CH_3CO.CH:CO$, as it dissolves in water to form acetoacetic ester, reacts with aniline to form anilido-acetoacetic ester, and with phenyl hydrazine to form the hydrazone of phenyl hydrazido-acetoacetic acid, whilst caustic baryta converts it into an acetate.

$$CH_3.CO.CH:CO - \begin{array}{l} \xrightarrow{H_2O} \quad CH_3.CO.CH_2.COOH \\ \xrightarrow{C_6H_5NH_2} \quad CH_3.CO.CH_2.CONHC_6H_5 \\ \xrightarrow{C_6H_5N_2H_3} \quad CH_3.C(:N.NHC_6H_5).CH_2CONHNHC_6H_5 \end{array}$$
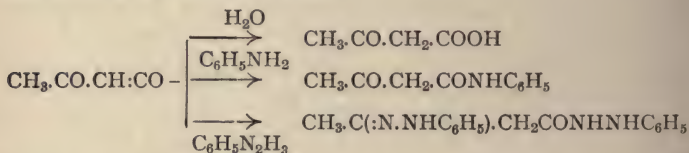
Thus acetyl keten shows to acetoacetic ester the relation of keten to acetic acid, and on this account is, according to Wilsmore, to be formulated as shown. On the other hand Staudinger is opposed to this open chain structure on account of the general chemical inertness of acetyl keten, and considers that all ketens form bimolecular polymerides, which are cyclobutane derivatives, acetyl keten being consequently formulated as a Δ^1-cyclobuten-1-ol-3-one.

$$\begin{array}{l} CO—CH_2 \\ | \qquad | \\ CH = C(OH) \end{array}$$
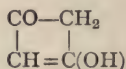
As regards the formula of keten itself, an alternative is suggested in $CH : C(OH)$, but this seems to be negatived by the fact that the usual reagents employed for detecting hydroxyl groups (potassium, sodium, phenyl carbimide) have no action on it, hence the hydroxyl group is not present. The somewhat recently

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[1] Schmidlin and Bergmann (*Ber.* 1910, **43**, 2821) have recently shown that keten is stable at moderately high temperature, and can be obtained by passing the vapour of acetone through a hard glass tube filled with porous earthenware and heated to 500-600° C. The yield of keten obtained in this manner is about 14 per cent., and the decomposition of the acetone may be represented by the following equation :—

$$2CH_3COCH_3 = 2CH_2:CO + 2CH_4.$$
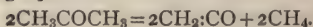
isolated carbon suboxide, C_3O_2, may be included among the ketens. This compound was first obtained in 1906 by Diels and Wolff as a sequel to the earlier work of Diels on the behaviour of nitrogen tricarboxylic ester with phosphorus pentoxide. This nitrogen carboxylic ester is formed by the interaction of chlorocarbonic ester with urethane, in the presence of sodium, and, when heated with phosphorus pentoxide, decomposes into ethylene, carbon dioxide, water, and ethyl carbimide carboxylate—

$$2Cl.COOR + NH_2COOR + 2Na = N(COOR)_3 + 2NaCl + H_2$$
$$N(COOC_2H_5)_3 = 2C_2H_4 + CO_2 + H_2O + OC:N.COOC_2H_5$$
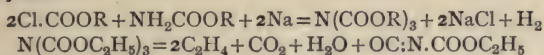
This decomposition led to the investigation of the action of phosphorus pentoxide on other esters, and it was found that malonic ester and oxalacetic ester both yielded ethylene and the new oxide of carbon.

$$CH_2(COOC_2H_5)_2 = 2C_2H_4 + H_2O + C_3O_2$$
$$\begin{array}{l} CO.COOC_2H_5 \\ | \qquad\qquad\qquad = 2C_2H_4 + CO + 2H_2O + CO_2 \\ CH_2.COOC_2H_5 \end{array}$$
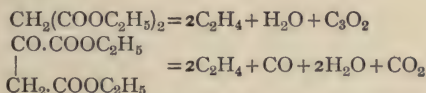
At a later date Staudinger showed that it could be obtained in small yield by the action of silver oxide on malonyl chloride,

$$CH_2(COCl)_2 + Ag_2O = 2AgCl + H_2O + C_3O_2,$$
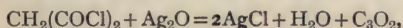
and in good yield by the action of zinc on dibromo-malonyl chloride (cf. prep. of ketens),

$$CBr_2(COCl)_2 + 2Zn = ZnCl_2 + ZnBr_2 + C_3O_2$$
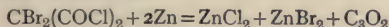
It is a mobile refractive liquid which boils at 7° C. and possesses a smell resembling that of a mustard oil. It may be solidified by cooling, the solid melting at − 107 to − 108° C. It burns with a smoky blue flame, to form carbon dioxide. In its general behaviour it appears to be an internal anhydride of malonic acid, since it combines with water to yield malonic acid, with hydrochloric acid to malonyl chloride, with primary amines to amides of malonic acid, and with ammonia to malonamide.

$$CH_2(COOH)_2 \xleftarrow{2H_2O} OC:C:CO \xrightarrow{2HCl} CH_2(COCl)_2$$
$$CH_2(CONHR)_2 \xleftarrow{2RNH_2} \quad\quad \xrightarrow{2NH_3} CH_2(CONH_2)_2$$
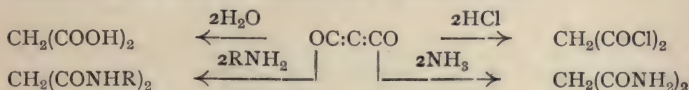
Carbon suboxide has little or no tendency to combine with

aldehydes, hydrogen cyanide, etc., but forms addition products with formic and acetic acids, the former behaving as if it were a dihydroxy-diolefine carboxylic acid of structure.

$$HOOC(HO)C:C:C(OH)COOH$$

The addition product formed with acetic acid decomposes, when heated, into acetic anhydride, and a syrup which passes into malonic acid on treatment with water. This latter reaction seems to point to the syrupy liquid as being a polymerized form of carbon suboxide. Liquid carbon suboxide decomposes at ordinary temperature, a dark red solid, soluble in water, being gradually formed. This substance approximates in composition to the original liquid. The decomposition is instantaneous at 100°C., carbon monoxide being evolved and a dark product remaining, which contains less oxygen than carbon suboxide.

The molecular formula, C_3O_2, has been established by combustion with copper oxide, by molecular weight determination according to Hofmann's vapour density method, and by explosion with oxygen and measurement of the amount of carbon dioxide formed. These results, taken in conjunction with the reactions of the oxide, have led Diels to formulate it as

$$OC:C:CO.$$

Michael, on the other hand, considers such a formula improbable, and points out that when the elimination of water occurs, with the possibility of ring formation, the change usually follows an unsymmetric course, as, for example, in acetonylacetone, where dehydration leads to the formation of dimethylfuran, and *not* to a dimethyl-diacetylene.

$$CH_3.CO.CH_2.CH_2.CO.CH_3 \quad or \quad \underset{\underset{OH}{|}}{CH_3.C{:}CH}.\underset{\underset{OH}{|}}{CH{:}C.CH_3} \quad \longrightarrow$$

$$H_2O \quad + \quad \overset{CH\text{------}CH}{\underset{CH_3.C\text{---}O\text{---}C.CH_3}{\parallel \qquad \parallel}}$$
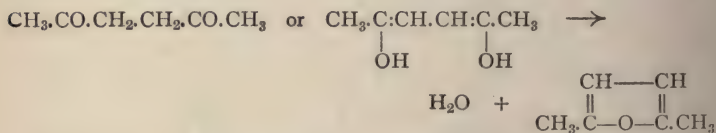
Following this idea, Michael considers that the oxide should be represented as the lactone of β-hydroxypropiolic acid, and explains its formation thus :—

$$H_2C(COOR)_2 \quad \rightarrow \quad \begin{array}{c} HC = C.OR \\ | \quad\quad | \\ CO\!-\!C \end{array} \quad \rightarrow \quad \begin{array}{c} C \equiv C \\ | \quad | \\ CO\!-\!O \end{array}$$
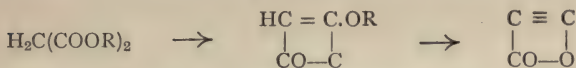
Diels, however, considers that his formula is the more correct for the following reasons—(1) the low boiling-point of the oxide, (2) the similarity of the oxide to the metallic carbonyls, (3) the high values of its molecular refraction and dispersion, (4) that it combines with four atomic proportions of bromine, (5) that water converts it into malonic acid, and (6) the improbability of the existence of a β-lactone containing the grouping $-C : C-$.

Finally, it may be pointed out that Staudinger's preparation of the oxide, by the general method employed for the formation of ketens, seems definitely to prove its keten structure, and consequently to disprove Michael's formula.

Ozonides—The use of ozone as an oxidizing agent has been known for some time, but it was left for Harries to show that it could be used for the preparation of complex aldehydes, and for the determination of the constitution of various unsaturated acids and hydrocarbons. In the preparation of ozonides, the substance to be examined is dissolved in a non-dissociating solvent, such as chloroform, and a current of ozonized oxygen, mixed with carbon dioxide, is passed into the solution at a low temperature. By working under these conditions the danger of accidents is lessened, the risk of explosions is minimized, and, of course, any volatile products are removed by the current of gas. The most important results were obtained with compounds containing an ethylenic linkage, such substances uniting with one molecule of ozone to form ozonides, which are usually thick oils or syrups of suffocating odour, and often of explosive character.

These ozonides are formulated either as containing the grouping—

$$\begin{array}{ccc} :C\!-\!\!-\!\!-\!\!-\!C: & & :C\!-\!C: \\ | \quad\quad\quad | & \text{or} & | \quad | \\ O\!-\!O\!-\!O & & O\!-\!O \\ & & \| O \| \end{array}$$
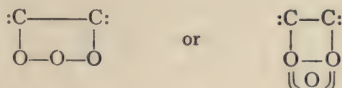
and in general behaviour somewhat resemble the peroxides, in that they liberate iodine from potassium iodide and bleach both potassium permanganate and indigo. They are decomposed by

water, usually into aldehydes and ketones and peroxides of these, or hydrogen peroxide, the point of fission being the position of the ethylenic linkage in the original unsaturated compound, hence their use as aids in the determination of constitution. The typical decomposition is thus represented—

$$:C — C: \qquad \longrightarrow \qquad :CO + :CO:O,$$
$$\underset{O.O.O}{|\quad|}$$

an example of which is seen in the case of the hydrocarbons of type $R.C(CH_3):CHR$, the ozonide on decomposition by water yielding an aldehyde and a ketone peroxide.

$$R.C(CH_3):CHR \xrightarrow{O_3} \begin{array}{c} RC(CH_3).CHR \\ |\_O_3\_| \end{array} \xrightarrow{H_2O} RC(CH_3):O:O + R.CHO$$
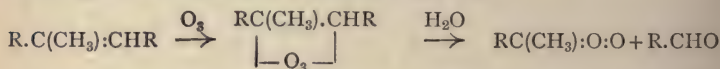
The method has been applied to the determination of the constitution of the so-called ozobenzene, a white amorphous mass produced by the action of ozone on benzene. This explodes violently when brought into contact with hot water, but Harries and Wein showed that if it were very carefully warmed with water, it decomposed with production of glyoxal ($OHC.CHO$), and is consequently to be regarded as benzene oxonide.

It is found that substances containing a carbonyl group (*e.g.* aldehydes, ketones, and monobasic acids) react under the above conditions in such a manner that they combine with four atoms of oxygen, and yield compounds which are termed ozonide-peroxides. These ozonide-peroxides are also decomposed by water, the decomposition resulting in the production of aldehydes and ketones (or their peroxides) as shown above, the excess oxygen being liberated in the form of hydrogen peroxide. Thus mesityl oxide ozonide peroxide yields bimolecular acetone peroxide, methyl glyoxal, and hydrogen peroxide,

$$(CH_3)_2C:CH.CO.CH_3 \xrightarrow{4O} (CH_3)_2.C—CH.CO(:O).CH_3$$

$$\underset{\underset{H_2O_2 + [(CH_3)_2C:O:O]_2 + CH_3.CO.CHO}{\downarrow H_2O}}{\underline{\quad O_3 \quad}}$$

whilst oleic acid ozonide peroxide yields pelargonic aldehyde, the semi-aldehyde of azelaic acid and hydrogen peroxide.

$$C_8H_{17}CH—CH.(CH_2)_7.CO_3H \xrightarrow{2H_2O} 2H_2O_2 + C_8H_{17}CHO + OHC.(CH_2)_7.COOH$$

$$\underline{\quad O_3 \quad}$$

Pelargonic   Azelaic acid
aldehyde   semi-aldehyde

These reactions have been applied to the determination of the constitution of many unsaturated acids and hydrocarbons. Thus in the case of oleic acid above, Harris is of the opinion that the ozonide peroxide is first formed, since the product, when washed with water and sodium hydrogen carbonate, yields the normal ozonide, whilst the aqueous solution shows the properties of hydrogen peroxide. The normal ozonide may be obtained if the oleic acid be first dissolved in acetic acid and then ozonized, the solution diluted with water, and neutralized with sodium hydrogen carbonate. Molinari in 1906 also showed that the normal ozonide could be obtained by the direct action of ozone on oleic acid in the absence of a solvent, and proceeded to study the decomposition products of the ozonide with the idea of establishing the constitution of the acid. He showed that the decomposition of the ozonide by alkali gave four acids, namely, azelaic acid, $HOOC.(CH_2)_7COOH$; normal nonylic acid, $CH_3(CH_2)_7COOH$; a monobasic acid, $C_{18}H_{36}O_3$, which is probably $[CH_3(CH_2)_7]_2.C(OH).COOH$; and a dibasic acid, $C_{18}H_{32}O_6$, together with a neutral substance, the composition of which was not ascertained. These results point to the fact that the ethylenic linkage in the oleic acid molecule is situated between the ninth and tenth carbon atoms, thus confirming the earlier work of Baruch. Harries, in a later paper, disputes the correctness of some of Molinari's work, and asserts that oleic acid ozonide, after washing with sodium hydrogen carbonate solution and water.

has a definite composition, and when decomposed by water yields products containing only nine and *not* eighteen atoms of carbon. He further states that the production of hydrogen peroxide by the decomposition of the ozonide with water is confirmed, and that the primary products of the reaction are aldehydes or their peroxides, which are transformed into acids by a secondary reaction. The decomposition products as found by Harries are nonaldehyde peroxide, $C_9H_{18}O_2$ (which is decomposed by water into nonaldehyde and hydrogen peroxide); pelargonic acid, $C_8H_{17}COOH$; and the semi-aldehyde of azelaic acid, $OHC(CH_2)_7COOH$, the production of which, of course, points to the ethylenic linkage in oleic acid as being between the ninth and tenth carbon atoms, *i.e.* $C_8H_{17}CH : CH(CH_2)_7COOH$.

In the case of various hydrocarbons it has been found that benzene yields a triozonide (see above) (I), diphenyl a tetra-ozonide (II), and naphthalene a diozonide (III), the formation of the latter indicating a difference in the structure of the two nuclei of the naphthalene molecule.

(I)   (II)   (III)
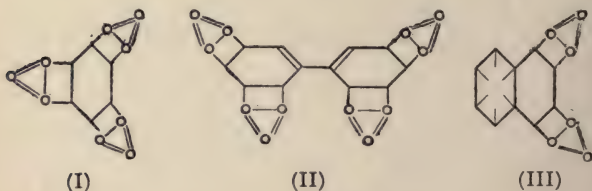
The ozonides of unsaturated hydroaromatic compounds are distinguished from those of the open chain compounds and those of the aromatic series by their great stability in the presence of water, thus the ozonide of tetrahydrobenzene is only slowly transformed, on long boiling with water, into *n*-adipic acid and its aldehyde.
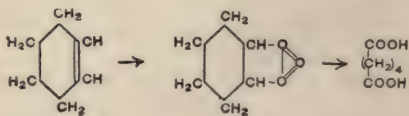
The simplest ozonide yet obtained is ethylene ozonide, $C_2H_4O_3$, which is formed when a current of ozonized air is passed into a solution of ethylene in methyl chloride at low temperature. It is a colourless liquid of an unpleasant, very pungent odour, and boils at $18°$ (16 mm.). It explodes violently when heated, or on rubbing with a glass rod. Molecular weight determinations show that it corresponds to the molecular formula, $C_2H_4O_3$. When decomposed by water the reaction proceeds in two different ways, yielding formaldehyde and hydrogen peroxide on the one hand, and on the other formic acid and formaldehyde, thus :—

$$C_2H_4O_3 \quad + H_2O = 2HCHO + H_2O_2$$
$$C_2H_4O_3 = HCHO + HCOOH$$
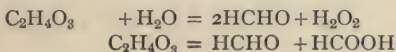
Among the rare aldehydes, the preparation of which has been rendered easier by the decomposition of ozonides, may be mentioned *pure* glyoxal, laevulinic aldehyde, the semi-aldehyde of succinic acid (β-aldehydropropionic acid), pyruvic aldehyde (methyl glyoxal), and mesoxalic dialdehyde.

Pure glyoxal is obtained when the ozonide of cinnamic aldehyde is decomposed by water.

$$C_6H_5.CH\!-\!CH.CHO \xrightarrow{H_2O} C_6H_5.CHO + OHC.CHO$$
$$\lfloor O_3 \rfloor$$
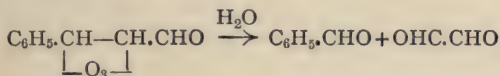
The product after removal of benzaldehyde is evaporated *in vacuo* at $25°$ C. and dried at $100°$ C., when a yellow amorphous mass, which is probably a threefold polymer of glyoxal, $(OHC.CHO)_3$, is obtained. This polymer when heated over phosphorus pentoxide yields the unimolecular glyoxal in the form of a pure yellow crystalline solid, which melts at $15°$ C. Pyruvic aldehyde is obtained by the decomposition of mesityl oxide ozonide (see above), the product obtained after removal of acetone peroxide being a fourfold polymer $(C_3H_4O_2)_4$.

Mesoxalic dialdehyde is obtained from phorone, which yields a diozonide on treatment with ozone.

$$(CH_3)_2C\!-\!CH.CO.CH\!-\!C(CH_3)_2 \xrightarrow{H_2O} 2[(CH_3)_2{:}C{:}O{:}O]_2 + OHC.CO.CHO$$
$$\lfloor O_3 \rfloor \qquad \lfloor O_3 \rfloor$$
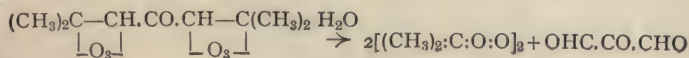
The acetone peroxide which is simultaneously formed is removed and the residual liquid concentrated under reduced pressure and finally dried *in vacuo*, when a glassy mass, consisting of a hydrate of mesoxalic dialdehyde, is obtained. This mass, when heated over phosphorus pentoxide at 65° C., yields a yellow compound possessing the composition of the anhydrous dialdehyde, but is probably a polymeride.

The semialdehyde of succinic acid is formed by the decomposition of allylacetic acid ozonide,

$$\begin{array}{c} \text{——CH}_2 \\ | \\ \text{O}_3 \quad | \\ | \\ \text{——CH.CH}_2.\text{CH}_2.\text{COOH} \end{array} \xrightarrow{\text{H}_2\text{O}} \text{OHC.CH}_2.\text{CH}_2.\text{COOH} + \text{HCHO},$$
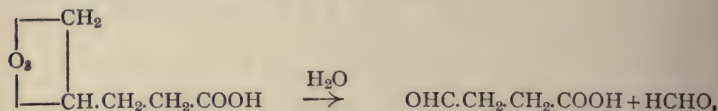
formic acid and succinic acid being simultaneously produced. The semi-aldehyde is an easily oxidizable oil, which on keeping, solidifies to a white crystalline mass of melting-point 147°. Molecular weight determinations show the oil to be a unimolecular compound, whilst the crystalline solid is bimolecular. Since the bimolecular compound is very stable towards oxidizing agents, Harries is of the opinion that condensation has taken place between the two carbonyl groups, and the compound is to be represented as—

$$\begin{array}{c} \text{HOOC.CH}_2.\text{CH}_2.\text{CH——O} \\ | \quad\quad | \\ \text{O——CH.CH}_2.\text{CH}_2.\text{COOH} \end{array}$$
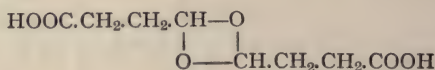
The crystalline variety passes back into the oily form when distilled at 134-136° C. (14 mm.).

Laevulinic aldehyde is obtained from the ozonide of methylheptenone,

$$\begin{array}{c} (\text{CH}_3)_2\text{C————CH.CH}_2.\text{CH}_2.\text{CO.CH}_3 \\ |\text{—O}_3\text{—}| \\ \downarrow \text{H}_2\text{O} \\ (\text{CH}_3)_2\text{C:O:O} + \text{OHC.CH}_2.\text{CH}_2.\text{CO.CH}_3 \end{array}$$
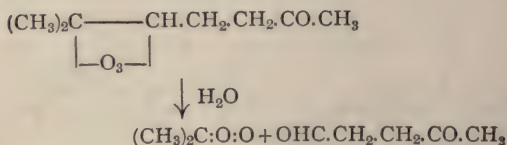
It is readily soluble in water, and reduces Fehling's solution in the cold. It does not polymerize, a fact which distinguishes it

from succinic aldehyde, which contains the carbonyl groups in the same relative positions. It is also obtained from the ozonide of Para caoutchouc, which was obtained by Harries as a white vitreous explosive solid of molecular composition, $C_{10}H_{16}O_6$. This ozonide, on treatment with water and subsequent distillation in steam, yields laevulinic aldehyde and its peroxide, together with some laevulinic acid. The reactions may be thus represented—

$$C_{10}H_{16}O_6 = \underset{\underset{O\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!O}{\|}}{O:C(CH_3).CH_2.CH_2.CH:O} + CH.CO.CH_2.CH_2.CHO.$$
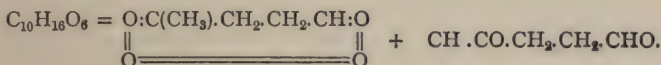
A similar result is obtained by use of the hydrocarbon, $C_{10}H_{16}$, which is obtained by the decomposition of gutta-percha, except that the yield of the aldehyde is diminished whilst that of the acid is increased. From these results Harries concludes that the parent hydrocarbons in the caoutchouc and the gutta-percha are identical, but that the ozonides are probably stereo-isomers, and that the reacting molecule is a 1.5-dimethylcyclo-octadiene.

$$\underset{\underset{HC.CH\;.CH_2.C.CH}{\|}}{CH_3.C.CH_2.CH_2.CH} \overset{O_3}{\longrightarrow} O_3\begin{array}{|c|} \hline -C(CH_3).CH_2.CH_2.CH- \\ \\ -CH.CH_2.CH_2(CH_3).C- \\ \hline \end{array}O_3$$
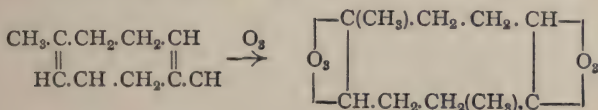
Molinari has tried to use ozone to distinguish between compounds containing an ethylenic linkage, and those containing an acetylenic linkage, for according to his results the latter class do not combine with ozone. Harries, however, considers that the results obtained and the conclusions drawn are incorrect, since certain compounds containing $C\equiv$ combine with ozone, more rapidly than compounds containing a $C=$ grouping, these ozonides on decomposition by water yielding acids—

$$-C\equiv C- \overset{O_3}{\rightarrow} \underset{\underset{-O_3-}{|\qquad|}}{.C\!\!=\!\!=\!\!C.} \overset{H_2O}{\rightarrow} -COOH + -COOH$$
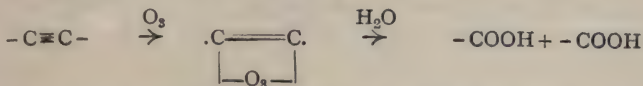
whilst it is also shown that both stearolic acid and phenylpropiolic acid form ozonides. This difference between the two observers may be explained, according to Harries, by the fact that Molinari

19

uses ozonized air, whilst Harries himself uses the presumably more energetic ozonized oxygen.

An interesting case of the behaviour of atmospheric oxygen in a manner analogous to ozone has been observed by Perkin and Salway, who found that β-methylhydrindone on exposure to atmospheric oxygen became converted into phthalic acid and benzylmethylketone-(o)-carboxylic acid. In this reaction it appears to be necessary to assume that the ketone is first transformed into the enolic form, which then forms an additive product with one molecule of oxygen, this product being broken down by the action of water thus—

$$
\begin{array}{c}
C_6H_4{-}CH_2 \\
| \qquad | \\
CO{-}CH.CH_3
\end{array}
\rightarrow
\begin{array}{c}
C_6H_4{-}CH_2 \\
| \qquad | \\
HO.C = C.CH_3
\end{array}
$$

$$
\downarrow O_2
$$

$$
\begin{array}{c}
CH_2COCH_3 \\
| \\
C_6H_4 \\
| \\
COOH \\
\text{Keto-acid}
\end{array}
\overset{H_2O}{\leftarrow}
\begin{array}{c}
C_6H_4{-}CH_2 \\
| \qquad | \\
HO.C{-}C.CH_3 \\
| \qquad | \\
O{-}O
\end{array}
$$
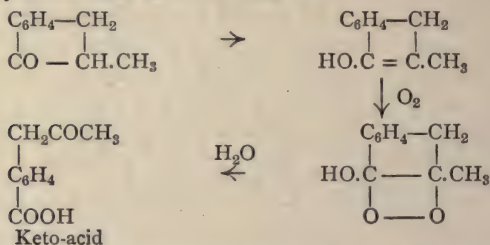
The keto-acid also assumes the enolic condition and gives the same series of transformations, resulting in the production of phthalic acid.

$$
\begin{array}{c}
CH_2COCH_3 \\
| \\
C_6H_4 \\
| \\
COOH
\end{array}
\text{ or }
\begin{array}{c}
CH{=}C(OH)CH_3 \\
| \\
C_6H_4 \\
| \\
COOH
\end{array}
\overset{O_2}{\rightarrow}
\begin{array}{c}
O{-}O \\
| \quad | \\
CH{-}C(OH).CH_3 \\
| \\
C_6H_4.COOH
\end{array}
$$

$$
\downarrow H_2O
$$

$$
C_6H_4(COOH)_2
\overset{O}{\leftarrow}
\begin{array}{c}
CHO \\
| \\
C_6H_4COOH
\end{array}
+ CH_3COOH
$$
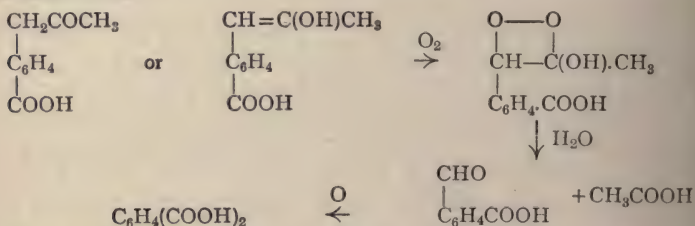
Triphenylmethyl.—In 1900 Gomberg, by the action of zinc on a solution of triphenylmethyl chloride in benzene, in absence of air, obtained a white crystalline solid, analysis of which yielded data corresponding to the empirical formula, $C_{19}H_{15}$. Molecular weight determinations by the cryoscopic method showed, however, that the substance corresponded to $C_{38}H_{30}$, that is $(C_{19}H_{15})_2$, or bimolecular triphenylmethyl, $[(C_6H_5)_3C]_2$, the first recorded exist-

ence of a compound containing carbon in the tervalent condition. The compound itself shows a characteristic unsaturated behaviour, in that it unites with the halogens, whilst it combines vigorously with oxygen to form a peroxide, $C_{38}H_{30}O_2$, which by the action of concentrated sulphuric acid is converted into triphenyl carbinol $(C_6H_5)_3C.OH$. It had been suggested that the bimolecular form might be hexaphenylethane, but Gomberg, in his earlier papers, considered this was improbable, since his compound had properties quite distinct from the ethane derivative as obtained by Ullmann and Borsum, and moreover was converted into it by the action of hydrochloric acid. The crystalline solid dissolves readily in organic solvents yielding yellow solutions, and Gomberg attributes this phenomenon to the presence of the free triphenyl methyl $[C_{19}H_{15}$ or $(C_6H_5)_3C-]$ ion, which possesses the properties of a univalent metal, confirmation of the latter fact being given in the ability of the halide derivatives to form perbromides and periodides. At a somewhat later date Gomberg showed that his new compound, which he concluded was the bimolecular form of triphenylmethyl, formed a series of additive compounds with hydrocarbons and esters, the latter being formulated as oxonium salts.

$$RCOOR' + [(C_6H_5)_3C]_2 \quad \rightarrow \quad [(C_6H_5)_3C]_2.\overset{\displaystyle OCR}{\underset{\displaystyle R'}{\overset{|}{\underset{|}{O}}}}$$

Ullmann and Borsum in 1902, with the idea that triphenylmethyl might be identical with hexaphenylethane, attempted to synthesize the latter compound by the action of zinc on triphenyl methyl chloride dissolved in glacial acetic acid, using zinc chloride as a condensing agent. They consider that the small amount of water in the glacial acetic acid converts the chloride into the carbinol, which is then reduced by the hydrogen liberated by the action of the zinc on the acid, thus—

$$(C_6H_5)_3C.Cl + H_2O = HCl + (C_6H_5)_3C.OH$$
$$2(C_6H_5)_3C.OH + 2H = 2H_2O + (C_6H_5)_3C.C(C_6H_5)_3,$$
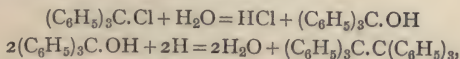
and since the compound so obtained was a stable substance, with

properties distinct from triphenylmethyl, they concluded that the identity of triphenylmethyl with hexaphenylethane was disproved.

A further investigation on Ullmann's compound was, however, carried out in 1904 by Tschitschibabin, who found that it was not hexaphenylethane, but was in all probability an isomer, of constitution

$$(C_6H_5)_3C.C_6H_4CH(C_6H_5)_2,$$

that is a (p)-benzhydryl tetraphenyl methane. This conclusion was arrived at by showing that the substance in question contained a methane hydrogen atom, since it yields a monobromo-derivative when brominated in carbon bisulphide solution in presence of sunlight, and the bromo-compound can be converted into the carbinol by the action of water in the presence of pyridine. The correctness of this view was shown in 1908, when Tschitschibabin synthesized Ullmann's compound from triphenyl methane and benzoyl chloride. These two substances, when condensed by the Friedel and Craft method, yield (p)-benzoyl triphenyl methane, which by the action of magnesium phenyl bromide and subsequent hydrolysis is converted into the tertiary alcohol (p)-benzhydryl triphenyl carbinol.

$$(C_6H_5)_3CH + Cl.CO.C_6H_5 \rightarrow (C_6H_5)_2CH.C_6H_4.CO.C_6H_5$$
$$\downarrow C_6H_5MgBr$$
$$(C_6H_5)_2CH.C_6H_4.C(OH)(C_6H_5)_2$$
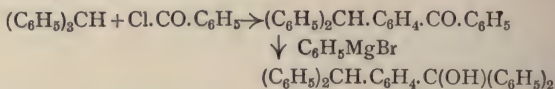
The hydroxyl group is then replaced by chlorine in the usual manner, and the chloro-derivative heated in boiling glacial acetic acid solution with aniline hydrochloride.

$$(C_6H_5)_2CH.C_6H_4.C(Cl).(C_6H_5)_2 + (H_2N.C_6H_5)HCl =$$
$$HCl + (C_6H_5)_2CH.C_6H_4C(C_6H_5)_2.C_6H_4NH_2.HCl.$$
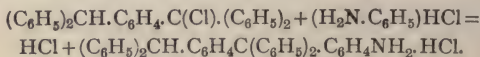
The amino-compound is diazotized and nitrogen eliminated in the usual manner, when Ullmann's compound is produced.

$$(C_6H_5)_2CH.C_6H_4C(C_6H_5)_2.C_6H_4NH_2 \longrightarrow (C_6H_5)_2CH.C_6H_4.C(C_6H_5)_3$$
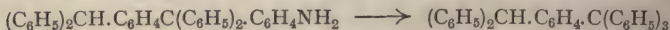
Thus it would seem that the probability of triphenmethyl being hexaphenylethane had not been disproved by Ullmann's work. Gomberg had rejected the hexaphenylethane hypothesis on the

grounds that both the tetra- and pentaphenylethanes were stable substances, and there seemed to be no reason why hexaphenylethane should be different from the other two, whereas triphenylmethyl is very reactive. Tschitschibabin has, however, pointed out that the remarkable activity of triphenylmethyl is not inconsistent with the structure of hexaphenylethane, since the presence of many electronegative groups in a compound leads to an increased activity of the compound, and he draws attention to the fact that the researches of Engler and others have shown that many substances react with atmospheric oxygen to form peroxides, as the first product of oxidation. The formation of Ullmann's compound from triphenylmethyl is assumed by Tschitschibabin to be due to an intermediate decomposition into triphenylmethane and triphenylmethyl chloride, which then react one with the other, with elimination of hydrochloric acid and production of (p)-benzhydryltetraphenylmethane.

$$(C_6H_5)_3C.C(C_6H_5)_3 + HCl = (C_6H_5)_3CH + (C_6H_5)_3C.Cl$$
$$(C_6H_5)_3C.Cl + C_6H_5.CH(C_6H_5)_2 = HCl + (C_6H_5)_3C.C_6H_4CH(C_6H_5)_2$$
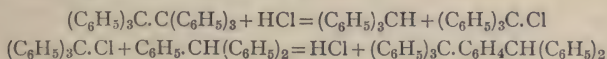
In 1905 Jacobson suggested a possible constitution, based on one given earlier by Heintschel, the latter investigator having proposed a di-quinonoid structure,

the difference being that Jacobson would make triphenylmethyl a combination of one quinonoid group with one non-quinonoid complex, thus :—

He argues that compounds of such type show a marked tendency to pass back into the aromatic condition, and shows that by the shifting of one hydrogen atom, such a compound would yield Ullmann and Borsum's hydrocarbon.
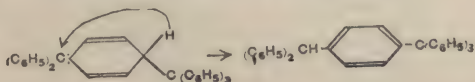
Again, he points out that if the aromatic group $(C_6H_5)_3C$ should detach itself, a quinonoid complex would remain, which could rearrange itself to the aromatic form by a shifting of linkages, and such a substance would thus act as triphenylmethyl.
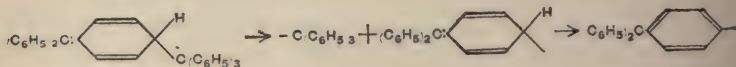
Gomberg has criticized this view, and points out that if it were correct then the parahalogen derivatives of the type—

should be capable of losing the chlorine atom marked * when acted upon by silver or zinc, and consequently give a compound formed by the linking up of two molecules of the original compound. This is not the case, for the derivatives obtained are considered to possess the same structure as triphenylmethyl, since they all give peroxides under similar conditions. This structure, however, cannot be $(ClC_6H_4)_3C -$, for such a configuration would require all these chlorine atoms to be of the same value, which is not the case, since the chlorine attached to one phenyl group is removable, showing that one phenyl group possesses functions different from the other two. Auwers has also pointed out the improbability of such a formula as Jacobson's, for he thinks that such a compound would be so unstable that it would rearrange itself as indicated in the following scheme :—
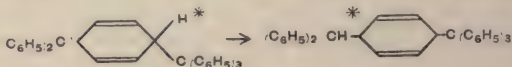
and as an argument in favour of this change mentions the case of methyl-dichloromethyl quinomethane, which spontaneously rearranges itself to (p)-methyldichloroethyl benzene.
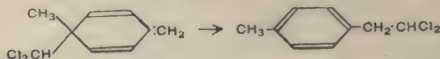
Since the heavy $- CHCl_2$ group wanders in this case into the

para-position, Auwers considers that the hydrogen atom indicated in Jacobson's formula would also do the same. Tschitschibabin also thinks that a quinonoid configuration is improbable, for Baeyer's work would seem to negative the quinonoid structure for the haloid derivatives; and since triphenyl methyl and its haloid derivatives are closely related, it would be hardly necessary to assume that the hydrocarbon itself possessed a quinonoid configuration. He also shows that the solid form is relatively stable, and may be retained for months in contact with dry air. This seems to render it necessary to regard it as being hexaphenylethane, or else to assume that a substance having a free valency is capable of existing in a condition of relative stability in the solid form, although in solutions in which its valencies are all neutralized in the normal manner it exhibits an enormous reactivity.

There seems at present to be strong presumptive evidence that the solid form is hexaphenylethane, but since the solid is colourless, whilst solutions of the hydrocarbon are yellow, it would appear that a different constitution is required for the dissolved hydrocarbon. No definite conclusions have as yet been reached regarding the solutions, but the following views have been suggested :—

1. The colour is due to ionization.

2. The solution contains $(C_6H_5)_2C : C_6H_4 : < \begin{array}{c} H \\ C(C_6H_5)_3 \end{array}$, which partly dissociates into a quinonoid cation, and a benzenoid anion.

3. The solution contains a quinonoid compound of the type indicated by Jacobson.

Finally, it may be mentioned that Schmidlin has suggested that triphenylmethyl is an equilibrium mixture of the two forms $(C_6H_5)_3C -$, and $(C_6H_5)_3C.C(C_6H_5)_3$, and has devised the following means of showing the relative proportions of the two forms. The yellow solution on shaking with air becomes colourless owing to the formation of the peroxide. The peroxide is insoluble in ether, so that an ether solution is shaken up with air, and after it becomes colourless the precipitate is filtered off, and the filtrate

now shaken again with excess of air and the precipitate again filtered. According to Schmidlin, the two precipitates will approximate to the proportions of the coloured and colourless varieties present in the original solution, and an experiment showed that the ratio was roughly one to ten.

Thus the question of constitution remains at present, but no doubt further investigations will be made, and the structure of this interesting compound will be finally settled in the near future.

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Triphenylmethyl.

Gomberg, *Ber.* 1900, **33**, 3150; 1901, **34**, 2726; 1902, **35**, 1822, 2397, 3914; 1903, **36**, 376; 1907, **37**, 1626, 2033, 3538; 1905, **38**, 1333, 2447; 1906, **39**, 1461, 2957, 3274; 1907, **40**, 1847; *J. Amer. Chem. Soc.* 1901, **23**, 496; 1902, **24**, 597; *Ann.* 1909, **370**, 142.

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[1] These two papers contain general resumés of the work on ozonides.

CHAPTER IX

THE GRIGNARD REACTION

THE use of organo-metallic compounds as synthetic reagents has, of course, been known for many years, but it appears to have been Barbier (in 1899) who pointed out that magnesium might be employed in the Saytzeff reaction, in place of zinc. In the following year Grignard published a general method for the preparation of alcohols and hydrocarbons by the condensation of magnesium alkyl or aryl halides in conjunction with various organic compounds.

Magnesium methyl iodide and magnesium dimethyl have, of course, been long known, but Grignard observed that in the presence of anhydrous ether, magnesium combines at ordinary temperature with alkyl or aryl iodides, with the appearance of brisk boiling, to form compounds of the type RMgX, which are soluble in an excess of ether. These compounds contain one molecule of ether, are not inflammable, and are very reactive.

In the preparation of the reagent, it is necessary to see that all the materials used are pure and dry, and it is found that the solution of the magnesium takes place more or less rapidly according to the nature of the halide compound used, and to the quantity of ether employed. The beginning of the reaction is frequently accelerated by the addition of a trace of iodine, or, as Baeyer found, by "activating" the magnesium, by warming it with about one-half its weight of iodine, so as to form a certain amount of magnesium iodide, care being taken to avoid melting of the mixture. It is probable that the formulation of the reagent as RMgX (R = alphyl or aryl radical, X = halogen) only represents the last stage in a series of reactions, and although such a type of compound is generally produced, it is found that secondary reactions occasionally take place, leading to the production of

hydrocarbons. This latter change is found to occur to a greater extent as the group R increases in complexity, benzyl chloride, for example, reacting with magnesium to yield more or less dibenzyl.[1]

$$2 \, C_7H_7Cl + Mg = MgCl_2 + C_{14}H_{14} \, [1]$$
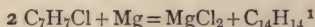
Experiment has shown that other solvents may be used in place of ethyl ether; thus Tschelinzeff found that it could be replaced by benzene, to which a small quantity of ether or anisole had been added, whilst benzene and xylene could be used alone provided a high enough temperature were employed. Methyl amyl ether, amyl phenyl ether, dimethylaniline, and other tertiary amines have also been used by various investigators.

Various views are held regarding the constitution of the complex formed between the magnesium organo-halide compounds and the ether, Baeyer and Villiger being of the opinion that an oxonium salt of type—

$$\begin{array}{c} MgR \\ | \\ (C_2H_5)_2O \\ | \\ X \end{array}$$
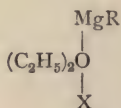
is produced, whilst, according to Tschelinzeff, the ether appears to act as a catalyst, anyhow at low temperatures, for he finds that if an inert solvent, such as benzene, be employed, a trace of ether added to the solution leads to the formation of the organo-magnesium halide. The change is represented thus :—

$$\begin{array}{c} R \\ | \\ (C_2H_5)_2O \\ | \\ X \end{array} \quad \xrightarrow{\mathrm{Mg}} \quad \begin{array}{c} Mg \, R \\ | \\ (C_2H_5)_2O \\ | \\ X \end{array}$$

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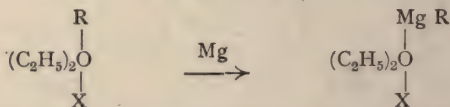
[1] In a recent communication to the Chemical Society, Kipping has pointed out that it is not really necessary to prepare the Grignard reagent first, and then bring it in contact with the other component of the reaction, but that equally good results may be obtained by mixing all the reaction substances together immediately. This method of procedure seems to diminish the amount of bye-products (e.g. dibenzyl, diphenyl, etc.) obtained, but it is also found that by working in this manner, no reaction can be obtained when acetone is one constituent of the mixture.

In the case of the inert solvent, it is found that anisole gives an even better result than ether, whilst a tertiary amine can also be used as catalyst, the intermediate stage being the production of a quinquevalent nitrogen compound, such as—

$$R'_3N(R).X$$
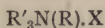
Blaise, who carried out some of the earlier work on the reaction, was also of the opinion that an oxonium salt was formed, and concluded that the basic character of the quadrivalent oxygen in such compounds increased with the increasing complexity of the alkyl groups, since the ethyl ether may be readily replaced by di-amyl ether in such compounds, but less readily by methyl amyl ether, or again it may be replaced by the more acidic phenyl ethyl ether. Finally, Tschelinzeff has prepared the compounds $RMgX.(C_2H_5)_2O$, and finds that two molecules of ether are combined with one of the organo-magnesium halide, the formation of such compounds being evident from the fact that on the addition of ether to a benzene solution of propyl iodide or isoamyl iodide containing magnesium, equal quantities of heat are evolved for each addition of the first two molecular proportions of ether added, the subsequent addition of ether causing little effect in this direction.

In the case of unsaturated alkyl halides it has been found that the reaction proceeds in a different manner, the product obtained being only slightly soluble in ether and containing two hydrocarbon residues combined with one atom of magnesium; thus, for example, with allyl iodide, the substance formed seems to possess the constitution $C_3H_5I.MgI.C_3H_5$. The products of this type are very unstable and do not react readily with aldehydes and ketones. As regards the method of procedure where the Grignard reaction is used, the magnesium is added in the form of wire, filings, or turnings, to the dry ether, and the halide compound usually dropped in through a tap-funnel. To complete the solution of the magnesium it is occasionally necessary to heat the ether. When the reaction is finished the contents of the vessel are cooled and the halide added, a vigorous reaction generally

taking place, the products of which separate usually as crystalline precipitates or thick oils. These are separated and decomposed either by ice-cold dilute sulphuric acid or acetic acid, the inorganic residue going into solution as a magnesium salt.

APPLICATIONS

One of the most important applications of the Grignard reagent is found in the reaction between it and compounds containing a carbonyl group, an additive compound resulting, which on decomposition by acid may lead to the formation of esters, ketones, alcohols, aldehydes, hydrocarbons, etc., according to the conditions of experiment. In the case of aldehydes and ketones the general reaction may be expressed as,

$$R.CHO \xrightarrow{R'MgX} RR'.CH(OMgX) \xrightarrow{H_2O} RR'.CHOH + MgX(OH)$$

$$R.R.CO \xrightarrow{R'MgX} RR.C(R').OMgX \xrightarrow{H_2O} RRC(R').OH$$
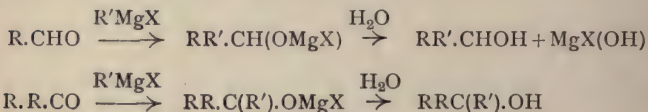
that, is the aldehyde yields a secondary alcohol whilst the ketone yields a tertiary alcohol. The yield of product in these cases is as a rule good, ranging from about 60-80 $\%$ of the theoretical amount. With unsaturated aldehydes or ketones containing a double linkage near the carbinol group it is found that as a rule the final product is an olefine hydrocarbon, which is produced by the dehydration of the alcohol that should result, an example of such a reaction being seen with β-naphthyl methyl ketone, which passes into unsymmetrical β-naphthyl methyl ethylene.

$$C_{10}H_7.CO.CH_3 \xrightarrow{MgCH_3I} [C_{10}H_7(CH_3)C(CH_3).OMgX]$$
$$\downarrow$$
$$C_{10}H_7(CH_3)C:CH_2 \leftarrow [C_{10}H_7(CH_3).C(CH_3).OH]$$
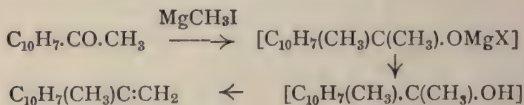
In the case of mesityl oxide and phorone it has been found that it is possible by working very carefully to isolate the intermediate carbinols.

$$(CH_3)_2C{:}CH.CO.CH_3 \xrightarrow{MgCH_3I} (CH_3)_2C{:}CH.C(OMgI)(CH_3)_2$$

Mesityl oxide

$$\downarrow H_2O$$

$$(CH_3)_2C{:}CH.C(CH_3)_2.OH$$

2.4-Dimethylpentene-3-ol-2

$$(CH_3)_2C{:}CH.CO.CH{:}C(CH_3)_2 \xrightarrow{MgCH_3I}$$

Phorone

$$\overset{OMgI}{\underset{CH_3}{(CH_3)_2C{:}CH.\overset{|}{\underset{|}{C}}.CH{:}C(CH_3)_2}}$$

$$\downarrow$$

$$\overset{OH}{\underset{}{(CH_3)_2C{:}CH.\overset{|}{C}(CH_3).CH{:}C(CH_3)}}$$

2.4.6-Trimethylheptadiene-2.5-ol-4
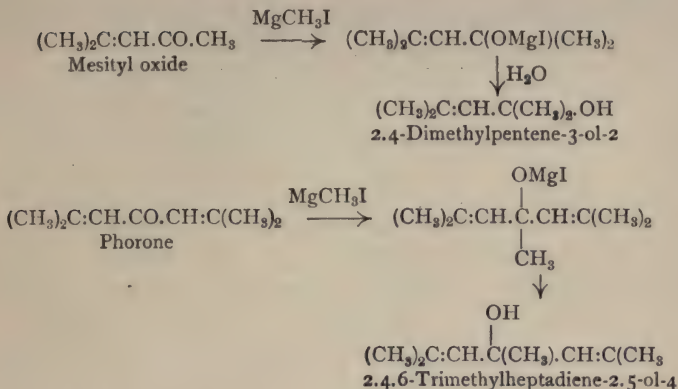
Grignard has shown that formaldehyde reacts normally, giving primary alcohols,

$$CH_2O + RMgX \;\rightarrow\; R.CH_2OMgX \xrightarrow{H_2O} R.CH_2OH.$$

but M. Tiffeneau in 1903 pointed out that polymerized formaldehyde reacts abnormally with magnesium benzyl bromide to yield (*o*)-tolyl carbinol, $CH_3.C_6H_4.CH_2OH$, and not benzyl carbinol, $C_7H_7CH_2OH$. He shows also that this is not due to the magnesium-benzyl halide behaving in an anomalous manner, since it is converted into phenyl acetic acid on treatment with carbon dioxide, but suggests that it may be a reaction of the type discovered by Manasse, in which formaldehyde on condensation with phenols, in the presence of alkali yields primary aromatic alcohols.

$$C_6H_5OH + CH_2(OH)_2 \;\rightarrow\; H_2O + HO.C_6H_4.CH_2OH(o \text{ and } p)$$

$$C_6H_5CH_2MgX + CH_2O \;\rightarrow\; HO.CH_2.C_6H_4.CH_2MgX$$

$$\downarrow$$

$$CH_3.C_6H_4.CH_2OH \;\leftarrow\; CH_3.C_6H_4CH_2.OMgX$$
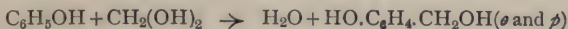
By a slight modification of the general process, ketones may be converted into αβ-unsaturated acids, the variation consisting in the use of an α-halogen fatty ester in the place of an alkyl halide.

$$RR'.CO + ICH_2.COOR + Mg \rightarrow RR'.C(OMgI).CH_2COOR$$

$$RR'.C:CHCOOR \leftarrow RR'.C(OH).CH_2COOR$$

Ketonic acids of the type of acetyl-succinic acid and acetyl-glutaric acid have been used by Simonsen, the products obtained with magnesium methyl iodide being terebic and terpenylic acids, the synthesis of which, in this manner, has definitely determined their structure. It must, of course, be understood that the acids in such a reaction are used in the form of esters in order to prevent reaction between the carboxyl group and the reagent—

$$\begin{array}{ccc} CH_3.CO.CH.COOR & \xrightarrow{MgCH_3I} & (CH_3)_2C(OMgI).CH.COOR \\ | & & | \\ CH_2.COOR & & CH_2.COOR \\ \text{Acetyl succinic acid} & & \downarrow H_2O \\ & & \\ (CH_3)_2.C\!\!-\!\!-\!\!-\!\!-\!\!CH.COOH & \xleftarrow{acid} & (CH_3)_2C(OH).CH.COOR \\ | \qquad\qquad | & & | \\ O\!-\!CO\!-\!CH_2 & & CH_2.COOR \\ \text{Terebic acid} & & \end{array}$$

$$CH_3CO.CH(CH_2COOR)_2 \xrightarrow{MgCH_3I} (CH_3)_2C(OMgI).CH(CH_2COOR)_2$$

$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow H_2O$$

$$\begin{array}{ccc} (CH_3)_2C\!\!-\!\!-\!\!-\!\!-\!\!CH.CH_2.COOR & \xleftarrow{acid} & (CH_3)_2.C(OH).CH(CH_2COOR)_2 \\ | \qquad\qquad | & & \\ O\!-\!CO\!-\!CH_2 & & \\ \text{Terpenylic acid} & & \end{array}$$
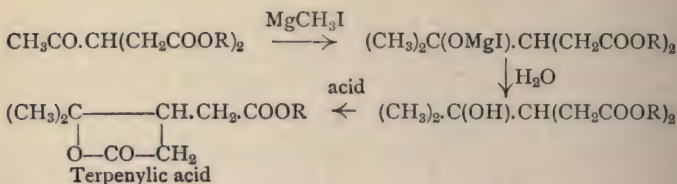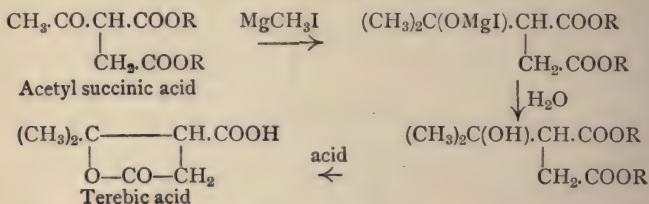
Kohler and his students have examined the behaviour of the Grignard reagent with unsaturated aldehydes and ketones containing the grouping $-C:C.C:O.R$, and have shown that the reactions depended on the nature of the atoms or groups associated with the ethylene carbon atom or carbonyl group. The nature of the addition appears to be determined by the following rules :—

1. In aldehydes ($R = H$) and ketones ($R = CH_3$), the organic magnesium compound reacts normally with the carbonyl group.

2. In ketones ($R = C_6H_5$), addition products are formed in the 1:4 position, thus with cinnamenyl phenyl ketone—

$$\underset{1\quad 2\quad 3\,4}{C_6H_5CH:CH.CO.C_6H_5} \xrightarrow{C_6H_5MgBr} C_6H_5.CH(C_6H_5).CH:C(OMgBr)C_6H_5.$$
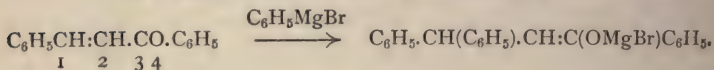
3. With unsaturated esters $(R = OR)$ either addition takes place as in (2) above, or the -OR group is replaced by an alkyl group, the former reaction taking place with aromatic and the latter with aliphatic magnesium compounds; for example, ethyl benzylidene malonate, when heated with magnesium phenyl bromide for a short time yields an addition product which is decomposed by water to form the substituted, ester shown.

$$C_6H_5CH : C(COOR)_2 \xrightarrow{MgC_6H_5Br} C_6H_5.CH(C_6H_5).\overset{\displaystyle COOR}{\underset{\displaystyle \downarrow H_2O}{C}} : C(OMgBr).OR$$
$$C_6H_5.CH(C_6H_5).CH(COOR)_2$$
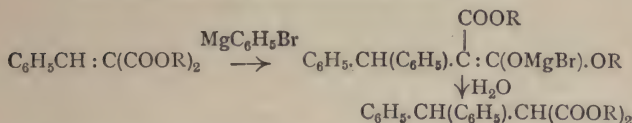
This ester, on acidification and boiling with water, loses carbon dioxide, and is converted into $\beta\beta$-diphenylpropionic acid.

$$C_6H_5.CH(C_6H_5).CH(COOH)_2 \rightarrow (C_6H_5)_2CH.CH_2.COOH + CO_2$$

The methyl ester of α-phenyl cinnamic acid reacts in a similar manner.

$$\underset{1 \quad 2 \quad 3 4}{C_6H_5.CH : C(C_6H_5).COOR} \rightarrow C_6H_5CH.\underset{\displaystyle C_6H_5}{\overset{\displaystyle |}{C}}(C_6H_5) : CO.\underset{\displaystyle MgBr}{\overset{\displaystyle |}{O}}R \xrightarrow{dry HCl}$$
$$(C_6H_5)_2CH.CH(C_6H_5).COOR$$
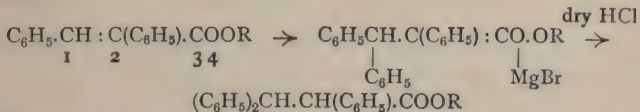
Esters react readily with the reagent, the normal course of the reaction resulting in the production of a tertiary alcohol, the various stages of the process being shown in the following scheme :—

$$\underset{\displaystyle OR'}{\overset{\displaystyle O}{R.\overset{\displaystyle \|}{C}}} \xrightarrow{R''MgX} \underset{\displaystyle OR'}{\overset{\displaystyle OMgX}{R.\overset{\displaystyle |}{C}.R''}} \xrightarrow{R''MgX} \underset{\displaystyle R''}{\overset{\displaystyle OMgX}{R.\overset{\displaystyle |}{C}.R''}} \xrightarrow{H_2O} \underset{\displaystyle R''}{\overset{\displaystyle OH}{R.\overset{\displaystyle |}{C}.R''}}$$
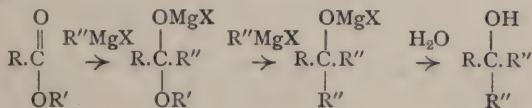
Many of the tertiary carbinols formed in this way are unstable, and lose water readily, passing into unsaturated compounds. This latter reaction takes place very readily if the carbinol be heated with acetic anhydride.

If formic ester be used in the above reaction, a secondary alcohol results, since it merely means the replacement of the radical R by a hydrogen atom. By using formic ester (3 mols.)

dissolved in dry ether cooled to $-50°$ C., and adding well-cooled magnesium phenyl bromide (1 mol.), Gattermann found that the reaction led to the formation of benzaldehyde.

$$C_6H_5MgBr + HCOOR \rightarrow C_6H_5CHO + BrMg.OR$$

Valeur, by application of magnesium phenyl halides to ethyl succinate, obtained tetraphenylbutane di-ol, which on heating with acetic acid passed in tetraphenyl tetrahydrofurane, by ring closing between the two hydroxyl groups.

$$\begin{array}{ccc} \text{ROOC.CH}_2 & \text{HO.C}(C_6H_5)_2\text{—CH}_2 & (C_6H_5)_2.\text{C—CH}_2 \\ | & \rightarrow \quad | & \rightarrow \quad | \quad O \quad | \\ \text{ROOC.CH}_2 & \text{HO.C}(C_6H_5)_2\text{—CH}_2 & (C_6H_5)_2.\text{C—CH}_2 \end{array}$$
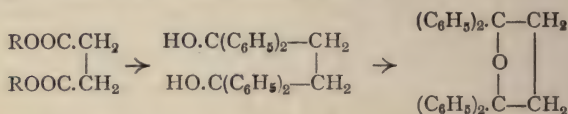
Grignard himself has obtained substituted glycollic acids by the action of magnesium methyl iodide on chloro-oxalic ester, adding the chloro-compound (1 mol.) to the magnesium organo-halide. By working in this manner the group -COCl is alone attacked.

$$\begin{array}{ccc} \text{COOR} & \text{2MgCH}_3\text{I.} & \text{COOR} \\ | & \rightarrow \quad \text{IMg.Cl} \; + & | \\ \text{COCl} & & \text{C(CH}_3)_2.\text{OMgI} \end{array}$$

$$\begin{array}{cc} & \text{COOR} \\ \text{ROOC.COCl} & | & +\text{I.Mg.Cl} \\ \rightarrow & \text{C(CH}_3)_2.\text{OCO.COOR} \end{array}$$

$$\begin{array}{c} \text{COOR} \\ | \\ \text{C(CH}_3)_2.\text{O.CO.COOR} \; + \; 3H_2O \; = \end{array}$$

$$\begin{array}{cc} & \text{COOH} \\ (CH_3)_2.\text{C(OH).COOH} \; + \; | & +2R.\text{OH} \\ & \text{COOH} \end{array}$$
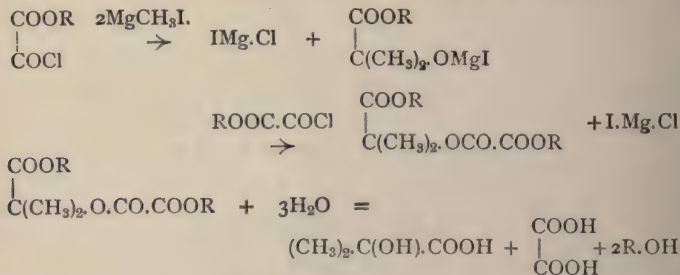
The esters of carbonic acid readily react with the reagent, the possible changes being represented by the following equations, as was shown by Tschitschibabin.

$$\begin{array}{lll} & \text{RMgX} & \text{H}_2\text{O} \\ A. \; \text{CO(OR)}_2 & \rightarrow \; \text{RC(OMgX)(OR)}_2 & \rightarrow \; \text{R.COOR} + \text{R.OH} + \text{HO.MgX} \\ B. \; \text{RC(OMgX)(OR)}_2 & \rightarrow \; \text{R}_2\text{C(OMgX).OR} + \text{X.MgOR} & \rightarrow \\ & & \text{R}_2\text{CO} + \text{R.OH} + \text{HO.MgX} \\ C. \; \text{R}_2\text{C(OMgX).OR} & \rightarrow \; \text{R}_2\text{C(OMgX)} + \text{X.MgOR} & \rightarrow \; \text{R}_3\text{C.OH} \end{array}$$
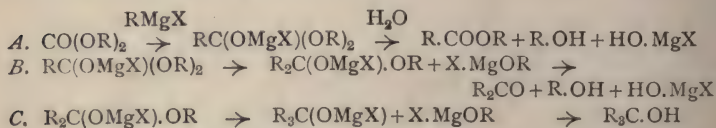
Hydrolysis of the addition products gives rise to esters, ketones,

and tertiary alcohols. The chief reaction is as shown in (A), and, provided the experiment is carefully carried out, may be stopped at that stage. The same investigator has shown that ortho-carbonic ester reacts in a similar manner, yielding as principal product the esters of an ortho-acid—

$$A. \quad C(OR)_4 \quad \xrightarrow{RMgX} \quad X.Mg.OR + RC(OR)_3$$
$$B. \quad RC(OR)_3 \quad \xrightarrow{RMgX} \quad X.Mg.OR + R_2C(OR)_2.$$
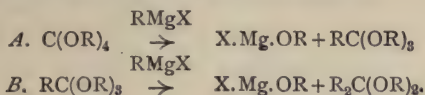
He also found that orthoformic ester reacts with the reagent, but that the action was only completed when the solvent ether was distilled off. In this way an acetal is formed, and may be converted into an aldehyde by hydrolysis with acid—

$$CH(OR)_3 \quad \xrightarrow{R'MgX} \quad R'CH(OR)_2 + X.Mg.OR \quad \xrightarrow{H_2O} \quad R'CHO + 2R.OH.$$
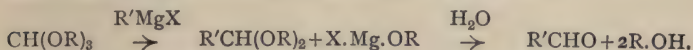
Bodroux also found that a good yield of benzaldehyde could be obtained by prolonged boiling of magnesium phenyl bromide with orthoformic ester, and subsequent hydrolysis of the acetal.

Blaise has used unsaturated esters of the type of methacrylic ester, and finds that one molecule of the organo-magnesium halide adds on to the ethylene linkage, whilst another molecule reacts with the —COOR group in the normal manner. Hydrolysis of the product yields a saturated ketone—

$$CH_2:C(CH_3).COOR \quad \xrightarrow{2MgCH_3I} \quad CH_3.CH_2.C(CH_3)(MgI).C(CH_3)(OMgI).OR$$
$$\downarrow H_2O$$
$$CH_3.CH_2.CH(CH_3).CO.CH_3 + R.OH + 2HO.MgI.$$
$$\text{Methyl pentanone}$$
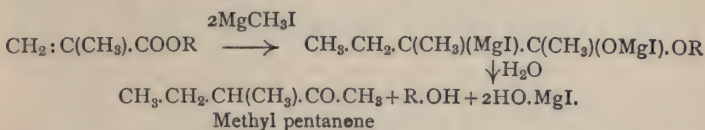
Ketonic acids, such as aceto-acetic ester, in which the possibility of a keto-enolic tautomerism exists, show an interesting behaviour with the reagent, in that, so far as they are enolic they decompose it, and as far as they are ketonic they react normally. Thus aceto-acetic ester reacts with magnesium methyl iodide to give a little methane and a product which, on decomposition with water, yields magnesium iodide and unchanged ester. If, however, the enolic formation be inhibited, as in ethyl aceto-acetic ester, then a normal type of reaction takes place, the

keto-group reacting, or, if an elevated temperature be employed, both the $>CO$ and $-COOR$ groups taking part in the change.

$$(CH_3)_2C(OH).CH(C_2H_5).C(CH_3)_2.OH \left. \begin{array}{c} \\ + \text{ unchanged ester} \end{array} \right\} \overset{110^\circ}{\longleftarrow} CH_3.CO.CH(C_2H_5).COOR$$

$$\text{MgMeI} \downarrow$$

$$\left\{ \begin{array}{c} (CH_3)_2.C(OH).CH(C_2H_5).COOR \\ + \text{ unchanged ester} \end{array} \right.$$
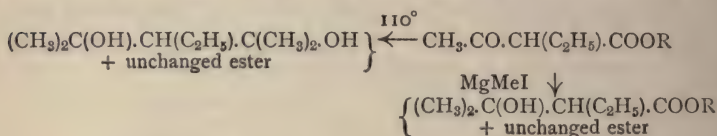
Acid chlorides and acid anhydrides react in a manner analogous to the esters, yielding tertiary alcohols—

$$R.COCl \overset{MgCH_3I}{\longrightarrow} RC(CH_3)(OMgI)Cl \overset{MgCH_3I}{\longrightarrow} RC(CH_3)_2.OMgI \overset{H_2O}{\longrightarrow} RC(CH_3)_2.OH$$

In this reaction the possibility of ketone formation also exists—

$$R.COCl + R'MgBr = Cl.MgBr + R.CO.R',$$
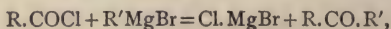
but where such a change happens the yield of ketone is usually small, the reaction proceeding further (as shown above) to the production of the tertiary alcohol. With acid anhydrides the stages of the change are possibly as shown in the subjoined scheme:—

$$(RCO)_2O \overset{R'MgX}{\underset{2R'MgX}{\longrightarrow}} RR'.C(OMgX)O.COR$$

$$2RR'C(OMgX)O.COR \longrightarrow 2R'_2R.C.OMgX + Mg(OCOR)_2 + MgX_2$$

$$R'_2R.C.OMgX + H_2O \longrightarrow R'_2R.C.OH + HO.MgX$$
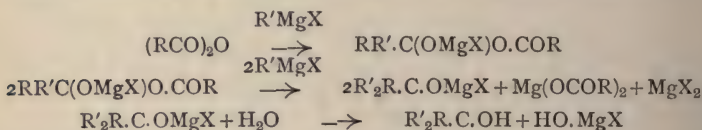
Carbonyl chloride similarly yields tertiary alcohols—

$$COCl_2 + 3RMgX \longrightarrow 2X.Mg.Cl + R_3.C.OMgX \overset{H_2O}{\longrightarrow} R_3.C.OH.$$
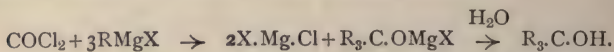
Houben found that if a solution of magnesium phenyl bromide in ether, be added to chlorocarbonic ester, the chief product of the reaction was ethyl benzoate, but if the ester be added to the organo-magnesium halide, then the chief product was triphenyl-carbinol, the following equations explaining the reaction in the two cases :—

$$C_6H_5MgBr + Cl.COOR \longrightarrow Cl.MgBr + C_6H_5COOR$$

$$C_6H_5COOR + 2C_6H_5MgBr \longrightarrow Br.MgOR + (C_6H_5)_3.C.OMgBr \overset{H_2O}{\longrightarrow} (C_6H_5)_3C.OH,$$
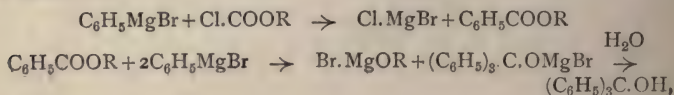
the benzoic ester undergoing normal ester reaction with the reagent. Numerous applications of the reagent have been made to nitrogen compounds, one of the earliest workers in this field being the French chemist Blaise, who showed that nitriles, α-cyano-acid esters, and phenyl carbimide readily react. Ketones are obtained in this way from the nitriles, the reaction proceeding best in the aromatic series; β-ketonic acids result from the cyano-acids, and anilides from the carbimides.

$$RCN + R'MgI \longrightarrow RR'C(:NMgI) \xrightarrow{2H_2O} R.CO.R' + NH_3 + I.Mg.OH$$

$$ROOC.CH_2.CN \xrightarrow{R'MgI} ROOC.CH_2.C(:NMgI)R'$$
$$\downarrow$$
$$ROOC.CH_2.CO.R' + NH_3 + I.Mg.OH$$

$$C_2H_5NCO \xrightarrow{R'MgI} C_6H_5N:C(OMgI).R' \longrightarrow [C_6H_5N:C(OH)R']$$
$$\downarrow$$
$$R'CO.NHC_6H_5$$
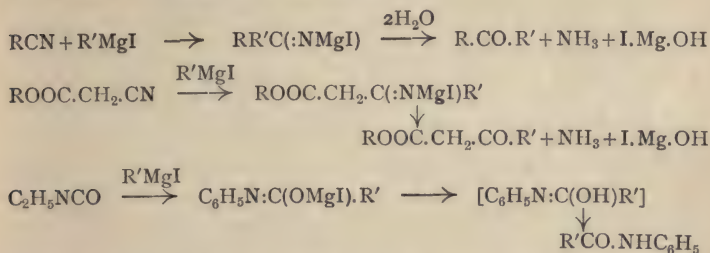
Sachs and Loevy have shown that mustard oils behave in the same way as the carbimides, giving thio-anilides, $RCS.NHC_6H_5$, whilst from the isonitriles they were able to obtain aldehydes.

$$CH_3NC \xrightarrow{C_6H_5MgBr} CH_3N:C(MgBr)C_6H_5 \xrightarrow{H_2O} CH_3N:CH.C_6H_5$$
$$\downarrow H_2O$$
$$C_6H_5CHO$$
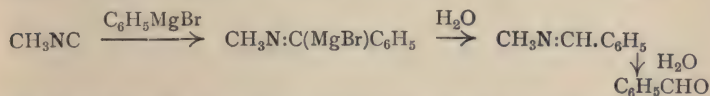
Sand and Singer, by using magnesium phenyl bromide and nitric oxide, have prepared nitroso-β-phenylhydroxylamine—

$$2NO + C_6H_5MgBr \longrightarrow NO.N(OMgBr).C_6H_5 \longrightarrow NO.N(C_6H_5)OH,$$
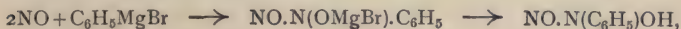
and Wieland extended the reaction to nitrogen peroxide, hoping to get nitroxylic acids, R.NOOH. Since, however, only β-substituted hydroxylamines were obtained, it seems apparent that the nitrogen peroxide must undergo reduction at some stage of the process.

Béis has used acid amides, and has found that on long boiling with an excess of the reagent they yield products from which ketones may be obtained by hydrolysis. This type of reaction has been carried further by Bouveault, who showed that substituted

formamides could be in a similar manner made to yield aldehydes.

$$R.CONH_2 \xrightarrow[\text{2R'MgX}]{\text{Béis}} R'H + RR'C(OMgX).NHMgX$$
$$\downarrow 2H_2O$$
$$R.CO.R' + Mg(OH)_2 + MgX_2 + NH_3$$

$$HCONRR' \xrightarrow[\text{R''MgX}]{\text{Bouveault}} R''CH(OMgX)NRR'$$
$$\downarrow H_2O$$
$$R''CHO + HO.MgX + NHRR'$$
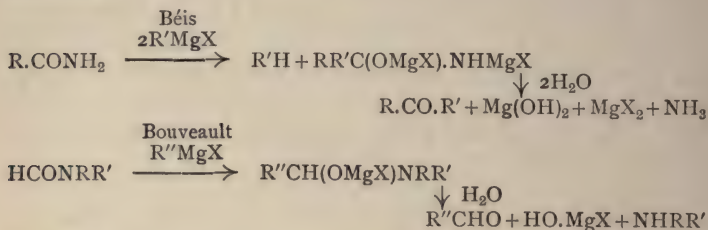
Various basic nitrogen compounds have been used by different observers, Sachs in 1905 showing that, with (p)-dimethylamino-benzaldehyde, the aldehydic oxygen atom could be replaced by two alkyl groups, when the product first obtained from the aldehyde and the reagent was heated at 100° C. with an excess of the reagent.

$$(CH_3)_2N.C_6H_4.CHO \xrightarrow{CH_3MgX} (CH_3)_2N.C_6H_4CH(OMgX).CH_3$$
$$\downarrow$$
$$\xleftarrow[\text{at 100°}]{CH_3MgX} (CH_3)_2N.C_6H_4.CH(OH).CH_3$$
$$\downarrow$$
$$HO.MgX + (CH_3)_2N.C_6H_4.CH(CH_3)_2$$
p-Isopropyldimethylaniline
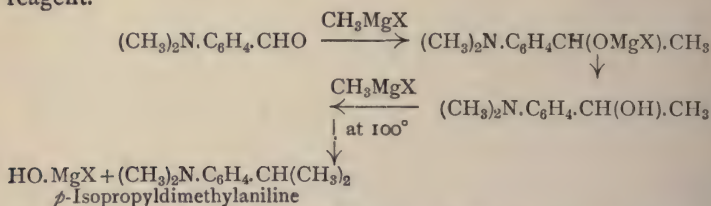
An important synthetical preparation of diazo-amines (triazens) has been devised by Dimroth, who has shown that mixed aromatic-aliphatic triazens can be obtained by the action of the reagent on organic azoimides, phenyl methyl triazen, for example, being prepared by adding phenyl azoimide to magnesium methyl iodide, and then bringing the mixture into aqueous ammonia and ammonium chloride at 0° C.

$$C_6H_5.N_3 + MgCH_3I + H_2O = HO.Mg.I + C_6H_5.N_3H.CH_3$$
Phenylmethyltriazen
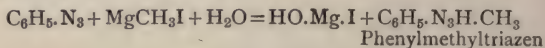
At a somewhat later date, the simple aliphatic diazoaminomethane or dimethyltriazen was similarly prepared from methylazoimide and magnesium methyl iodide. M. Busch has found that unsaturated alkylidene amines form addition compounds, which are decomposed by acid with production of anilino-benzenes.

$$C_6H_5CH:N.C_6H_5 \xrightarrow{\quad C_2H_5MgI \quad} C_6H_5(C_2H_5)CH.N(MgI).C_6H_5$$

$$\downarrow H_2O$$

$$HO.Mg.I + C_6H_5CH(C_2H_5).NHC_6H_5$$

$$\alpha\text{-Anilino-propyl benzene}$$
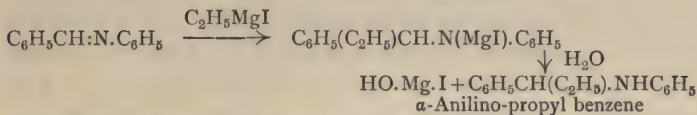
Amines containing available hydrogen react with the reagent in the same manner as simple hydroxylic compounds, yielding hydrocarbons.

$$H.OH + R.MgX \longrightarrow X.Mg.OH + R.H.$$
$$H\,NH_2 + R.MgX \longrightarrow H.NHMgX + R.H.$$
$$R'NH_2 + R.MgX \longrightarrow X.MgNHR' + R.H.$$

Houben has recently shown that methylaniline, when heated in dimethylaniline solution in a stream of carbon dioxide with magnesium and methyl iodide, yields (p)-dimethylaminobenzoic acid, the dimethylaniline probably acting as a methylating agent of the mono-methyl acid first formed.

$$C_6H_5NHCH_3 + CO_2 + Mg + CH_3I \longrightarrow CH_4 + N(CH_3).C_6H_5.COOMgI$$

$$\downarrow \text{rearrangement}$$

$$(CH_3)_2N.C_6H_4.COOMgI \xleftarrow{\quad \text{methylation} \quad} CH_3.NH.C_6H_4.COOMgI$$

$$\downarrow H_2O$$

$$(CH_3)_2N.C_6H_4.COOH$$
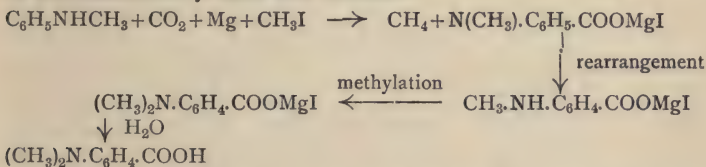
He further suggests that perhaps the first step in the reaction consists in the formation of a complex $IMg.C_6H_4.N(CH_3)_2$, from the interaction of the dimethyl aniline and magnesium methyl iodide, and this then reacts in the normal manner with the carbon dioxide—

$$(CH_3)_2N.C_6H_4.MgI + CO_2 \longrightarrow (CH_3)_2N.C_6H_4.COOMgI$$

$$\downarrow H_2O$$

$$(CH_3)_2N.C_6H_4.COOH.$$
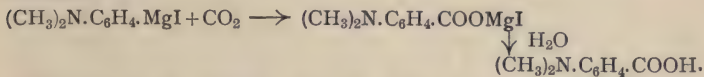
Occasionally the reagent acts as a reducing substance, Franzen having found that azobenzene reacts with magnesium ethyl bromide to yield butane and a compound from which, by hydrolysis, he obtained hydrazobenzene—

$$C_6H_5N_2C_6H_5 \xrightarrow{\quad 2C_2H_5MgBr \quad} C_4H_{10} + BrMg.N(C_6H_5).N(C_6H_5).MgBr$$

$$\downarrow 2H_2O$$

$$C_6H_5.NH.NH.C_6H_5 + 2Mg \begin{array}{c} \diagup Br \\ \diagdown OH. \end{array}$$
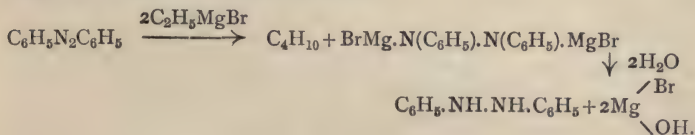
Beside the carbonyl and nitrogen compounds mentioned above, a large number of other substances have been used in connection with the Grignard reagent, some of the more important being here mentioned. Carbon dioxide unites directly with the reagent, the resulting product on hydrolysis yielding carboxylic acids—

$$RMgX + CO_2 \longrightarrow RCOOMgX \xrightarrow{H_2O} R.COOH + HO.MgX.$$
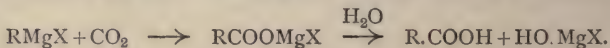
The preparation of acids in this way is, however, not always such a simple reaction as above illustrated, for if magnesium phenyl bromide be used, the reaction can be so adjusted that instead of benzoic acid being produced, benzophenone and triphenyl carbinol are obtained.

$$C_6H_5COOMgBr + 2C_6H_5MgBr \longrightarrow (C_6H_5)_2.C(OMgBr)_2 + C_6H_5MgBr$$
$$\downarrow H_2O$$
$$(C_6H_5)_2CO + 2HO.MgBr$$
$$C_6H_5MgBr \downarrow$$
$$(C_6H_5)_3.C.OH + HO.MgBr \xleftarrow{H_2O} (C_6H_5)_3.C.OMgBr + MgO + MgBr_2$$
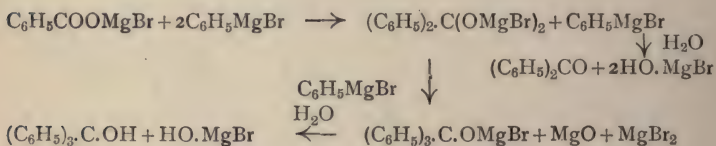
Carbon oxysulphide in a similar manner yields thio-acids,

$$COS + C_6H_5MgBr \longrightarrow C_6H_5CS.OMgBr \xrightarrow{H_2O} C_6H_5CS.OH + HOMgBr,$$
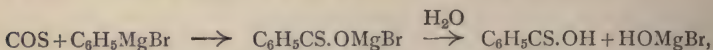
whilst Houben has recently shown that carbon bisulphide behaves in an analogous way, giving rise to compounds which he designates as carbithionic acids—

$$CS_2 + RMgX \longrightarrow RCS.SMgX \xrightarrow{H_2O} HO.MgX + RCS.SH.$$
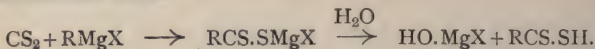
Various derivatives of glycol have been used, Grignard recently showing how, from glycol chlorhydrin, the higher fatty alcohols may be obtained. In this reaction the chlorhydrin is brought in contact with the reagent in the cold, and the resulting chloro-derivative, on decomposition with a second molecule of the reagent, yields a complex, which on hydrolysis is converted into the alcohol.

$$\underset{CH_2OH}{\overset{CH_2Cl}{|}} \xrightarrow[\text{cold}]{RMgX} RH + \underset{CH_2OMgX}{\overset{CH_2Cl}{|}} \xrightarrow{R'MgX'} Cl.MgX' + \underset{CH_2.OMgX}{\overset{R'.CH_2}{|}}$$
$$\downarrow H_2O$$
$$R'.CH_2.CH_2.OH + HO.MgX$$
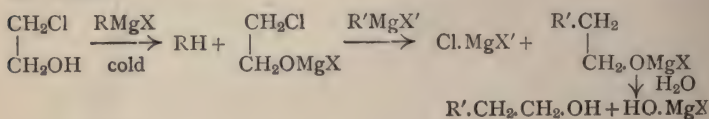
In the case of ethylene oxide and magnesium alkyl bromides, Blaise found that an oxonium salt was first produced. This salt, on removal of the solvent, isomerizes rapidly to the corresponding hydroxylic derivative, from which the alcohol may be prepared in the usual manner—

$$C_2H_4O \xrightarrow{\text{RMgBr}} C_2H_4O(MgBr)R \longrightarrow R.CH_2.CH_2.OMgBr$$
$$\downarrow$$
$$R.CH_2.CH_2.OH.$$
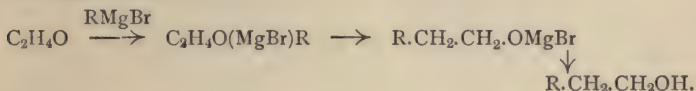
If, however, the addition product be subjected to the action of water, it decomposes, and the regenerated ethylene oxide, reacting with the magnesium bromide, simultaneously produced, yields a glycol bromohydrin derivative—

$$\begin{matrix} CH_2 \\ | \quad O \\ CH_2 \end{matrix} \xrightarrow{\text{MgBr}_2} \begin{matrix} CH_2Br \\ | \\ CH_2OMgBr \end{matrix} \longrightarrow \begin{matrix} CH_2Br \\ | \\ CH_2.OH. \end{matrix}$$
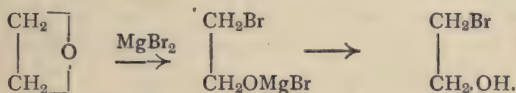
The simple homologues of ethylene oxide yield secondary alcohols,

$$\begin{matrix} R.CH.CH_2 \\ \lfloor_{O}\rfloor \end{matrix} \xrightarrow{\text{R'MgX}} \begin{matrix} R.CH.CH_2R' \\ | \\ OMgX \end{matrix} \xrightarrow{\text{H}_2\text{O}} \begin{matrix} R.CH.CH_2R' + HO.MgX \\ | \\ OH \end{matrix}$$
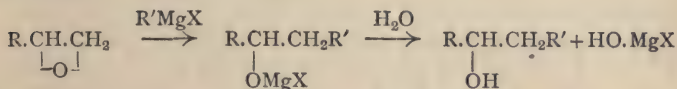
but the α-dialkyl derivatives react abnormally, the unsymmetrical members of the series behaving as if they first isomerized to aldehydes, and the symmetrical as though to ketones, reaction then taking place in the normal manner, the final products obtained being secondary and tertiary alcohols.

$$\begin{matrix} (CH_3)_2C\text{---}CH_2 \\ \lfloor_O\rfloor \end{matrix} \longrightarrow [(CH_3)_2.CH.CHO] \xrightarrow{\text{RMgX}} (CH_3)_2.CH.CHR.OH$$

$$\begin{matrix} R.CH\text{---}CH.R \\ \lfloor_O\rfloor \end{matrix} \longrightarrow [R.CH_2.CO.R] \xrightarrow{\text{R'MgX}} R.CH_2.C(OH).RR'.$$
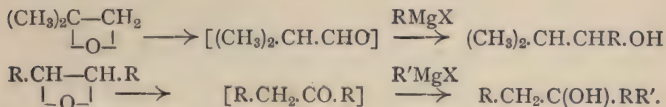
An interesting reaction was discovered by Zelinsky in 1902, when he found that the product of the action of magnesium on acetyl-(n)-butyl iodide, on decomposition with acetic acid, yielded 1-methyl cyclopentane-ol-1, probably due to rearrangement of the magnesium organo-halide compound first formed.

$$CH_3CO.(CH_2)_4.I \xrightarrow{\;g\;} CH_3CO.(CH_2)_4MgI$$

$$\begin{array}{ccc} CH_3.CH_2 & & CH_3.CH \\ | \quad\; \Big\downarrow & & | \\ | \quad C(CH_3)OMgI & \longrightarrow & | \quad C(CH_3)OH \\ | & & | \\ CH_2.C & & CH_2.CH_2 \end{array}$$

Kling has used the reagent to determine the constitution of acetol (acetyl carbinol), $C_3H_6O_2$, which may be represented as,

$$\text{(I)} \quad CH_3CO.CH_2OH \quad \text{or} \quad CH_3.\underset{\underset{O}{\rule{0.4cm}{0.4pt}}}{C(OH)\rule[0.5ex]{0.4cm}{0.4pt}CH_2} \quad \text{(II)}$$

and consequently should behave towards the reagent either as a keto-compound or as an ethylene oxide. By using the acetyl derivative and magnesium ethyl iodide an amylene glycol was obtained, which shows that acetol must be represented by (I)—

$$CH_3CO.CH_2OH \xrightarrow{\;MgC_2H_5I\;} CH_3(C_2H_5)C.(OMgI)CH_2OH$$
$$\downarrow H_2O$$
$$CH_3(C_2H_5)C.(OH)CH_2OH.$$

Tertiary alcohols may be prepared from the addition product of the reagent and carbon dioxide. After removal of excess of the carbon dioxide the product is brought into contact with a further quantity of the reagent in the cold, and the resulting product heated for some time on the water bath and then decomposed by acid—

$$RMgX \xrightarrow{\;CO_2\;} RCOOMgX \xrightarrow{\;R'MgX\;} CRR'(OMgX)_2$$
$$\downarrow R'MgX$$
$$CRR'_2(OMgX) + (MgX)_2O$$
$$\downarrow H_2O$$
$$RR'_2C.OH + HO.MgX.$$

Werner has produced aromatic hydrocarbons by the action of dimethyl-sulphate on the reagent, paraxylene resulting when magnesium tolyl bromide is thus treated—

$$C_7H_7MgBr + (CH_3)_2.SO_4 \longrightarrow CH_3.C_6H_4.CH_3 + CH_3SO_4.MgBr.$$

Mention may also be made of the extension of the reaction to the compounds of the naphthalene, anthracene, and acridine

series, β-naphthyl magnesium bromide reacting in the normal way with aromatic ketones.

$$C_{10}H_7MgBr + C_6H_5CO.C_6H_5 \longrightarrow (C_6H_5)_2C(C_{10}H_7).OMgBr$$
$$\downarrow H_2O$$
$$(C_6H_5)_2C(OH).C_{10}H_7$$
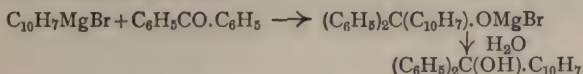
Anthraquinone with magnesium phenyl bromide yields γ-dihydroxy-γ-diphenyldihydroanthracene, whilst N-methyl acridone similarly yields hydroxyphenyl-N-methyl dihydroacridine.
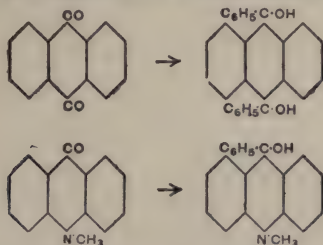
Behal has prepared substituted aldehydes from the ethers of α-glycols, these ethers resulting from the action of the reagent on such compounds as the ethyl ester of ethoxy-acetic acid. They are then converted into the aldehydes by heating with dry oxalic acid at $110°$-$115°$ C.

$$CH_2OR'.COOR \xrightarrow{RMgX} CH_2OR'.CR(OMgX).OR$$
$$\downarrow RMgX$$
$$CH_2OR'.CR_2(OMgX) + X.MgOR$$
$$\text{Dry oxalic} \downarrow H_2O$$
$$\text{acid}$$
$$R_2CH.CHO \leftarrow R_2C.CHOH \leftarrow R_2C:CHOR \xleftarrow{} CH_2OR'.CR_2.OH$$
$$110-115°$$
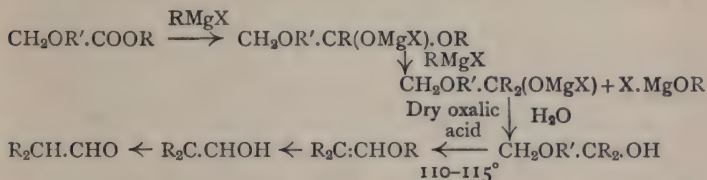
Sudborough has pointed out that the reaction between the reagent and a primary amine is, in the cold, quantitative, one molecule of methane being liberated for each molecule of magnesium methyl iodide used, thus—

$$RNH_2 + MgCH_3I = RNH.MgI + CH_4.$$
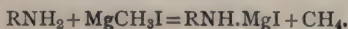
When heated, a second molecule of methane is liberated, the reaction perhaps occurring as shown in the following equation:—

$$RNHMgI + MgCH_3I = RN(MgI)_2 + CH_4.$$
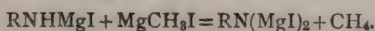
With secondary amines, only one molecule of methane is liberated, whilst tertiary amines do not enter into reaction.

$$R_2NH + MgCH_3I = R_2N.MgI + CH_4.$$
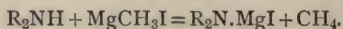
Hence it is suggested that this reaction might be used for the characterization and estimation of amines.

Perhaps the most important synthetical use made as yet with the Grignard reaction is that which led Perkin to prepare members of the terpene series, for details of which see Chapter II.

As thus far shown in the previous pages, the Grignard reaction has been used for the preparation in most cases of saturated compounds, but Klages has shown that by a modification of the conditions of reaction, unsaturated compounds can be obtained directly, in the aromatic series. Using an aromatic ketone, magnesium, and an alkyl iodide in equimolecular proportions, the normal course of the reaction is to yield a tertiary alcohol, but if the proportion of magnesium and alkyl iodide be doubled, and the whole reaction mixture heated for several hours, it is found that an unsaturated hydrocarbon is formed. Acetophenone, for example, under these conditions, yields β-allyl benzene when condensed with magnesium methyl iodide, presumably owing to the dehydration of the intermediately formed carbinol—

$$C_6H_5CO.CH_3 \longrightarrow [C_6H_5C(CH_3)_2.OH] \longrightarrow C_6H_5C(CH_3):CH_2.$$
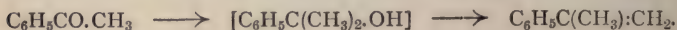
This appears to be a general reaction in the aromatic series, except when two ortho-substituents are present in the aromatic compound. Acetyl mesitylene, for example, is such a compound, and here, although the normal addition product is formed with the reagent, on decomposition with acid it yields unchanged acetyl mesitylene.

The magnesium alkyl iodides of the ketones were also found to react with dry ammonia to form derivatives which on decomposition by water yielded alkyl styrenes.

$$\begin{array}{ccc} & \text{MgCH}_3\text{I} & \text{NH}_3 \\ C_6H_5CO.CH_3 & \longrightarrow C_6H_5C(CH_3)_2.OMgI & \longrightarrow C_6H_5C(CH_3)_2.OMgNH_2 \\ & & \downarrow 2HO \\ H_2O + C_6H_5C(CH_3):CH_2 & \longleftarrow C_6H_5.C(CH_3)_2.OH + Mg(OH)_2 + NH_3 \end{array}$$
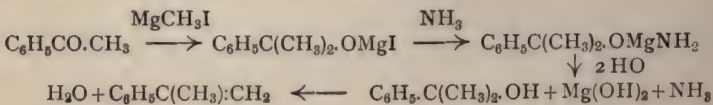
Stilbenes have been obtained by the action of magnesium benzyl chloride on aldehydes, anisaldehyde, for example, yielding p-methoxystilbene, and piperonal, the methylene ether of 3.4-dihydroxy stilbene.

$$CH_3O.C_6H_4.CHO \xrightarrow{MgC_7H_7Cl} [CH_3O.C_6H_4.CH(OH).CH_2.C_6H_5]$$
$$\downarrow$$
$$CH_3O.C_6H_4.CH:CH.C_6H_5.$$
$$CH_2O_2:C_6H_4CHO \longrightarrow CH_2O_2:C_6H_4.CH(OH)CH_2.C_6H_5$$
$$\downarrow$$
$$CH_2O_2:C_6H_4.CH:CH.C_6H_5.$$
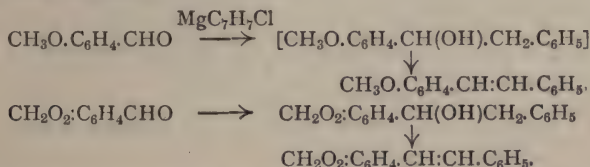
As final examples of the Grignard reaction may be mentioned Moureau's preparation of aldehydes of the acetylene series, and various transpositions of the Fittig and Wurtz type. The former are obtained from monosubstituted acetylenes by the action of the reagent, the intermediately formed magnesium compound then condensed with ortho-formic ester (see p. 305) and the resulting acetal hydrolyzed.

$$RC:CH \xrightarrow{C_2H_5MgBr} H.C_2H_5 + R.C:CMgBr$$
$$\downarrow HC(OR)_3$$
$$R.C:C.CHO + 2R.OH \xleftarrow{H_2O} R.C:C.CH(OR)_2 + Br.Mg.OR$$
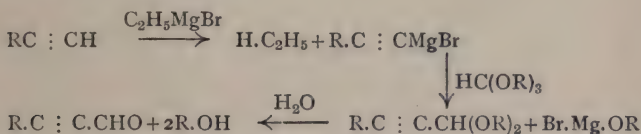
Of the Fittig and Wurtz type of reaction, the condensation of the reagent with alkyl halides and metal halides form the best examples, such reactions being illustrated in the subjoined equations—

$$R.Br + BrMgR = MgBr + R.R$$
$$SnBr_4 + 4MgC_6H_5Br = 4MgBr_2 + Sn(C_6H_5)_4$$
$$PbCl_4 + 4MgC_6H_5Cl = 4MgCl_2 + Pb(C_6H_5)_4.$$
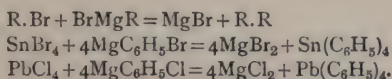
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INDEX OF AUTHORS

317

INDEX OF SUBJECTS

A

B

C